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THE MECHANISM OF HOMOGENEOUS ORGANIC REACTIONS FROM THE PHYSICAL-CHEMICAL STANDPOINT

BY

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American Chemical Society
Monograph Series

BOOK DEPARTMENT

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GENERAL INTRODUCTION

American Chemical Society Series of Scientific and Technologic Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in coöperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, Secretary of the American Chemical Society, Washington, D. C.; John E. Teeple, Treasurer of the American Chemical Society, New York City; and Professor Gellert Alleman of Swarthmore College. The Trustees have arranged for the publication of the American Chemical Society series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company of New York City.

The Council, acting through the Committee on National Policy of the American Chemical Society, appointed the editors, named at the close of this introduction, to have charge of securing authors, and of considering critically the manuscripts prepared. The editors of each series will endeavor to select topics which are of current interest and authors who are recognized as authorities in their respective fields. The list of monographs thus far secured appears in the publisher's own announcement elsewhere in this volume.

The development of knowledge in all branches of science, and especially in chemistry, has been so rapid during the last fifty years and the fields covered by this development have been so varied that it is difficult for any individual to keep in touch with the progress in branches of science outside his own specialty. In spite of the facilities for the examination of the literature given by Chemical Abstracts and such compendia as Beilstein's Handbuch der Organischen Chemie, Richter's Lexikon, Ostwald's Lehrbuch der Allgemeinen Chemie, Abegg's and Gmelin-Kraut's Handbuch der Anorganischen Chemie and the English and French Dictionaries of Chemistry, it often takes a great deal of time to coördinate the knowledge available upon a single topic. Consequently when men who have spent years in the study of important subjects are willing to coördinate their knowledge and present it in concise, readable form, they perform a service of the highest value to their fellow chemists.

It was with a clear recognition of the usefulness of reviews of this character that a Committee of the American Chemical Society recommended the publication of the two series of monographs under the auspices of the Society.

Two rather distinct purposes are to be served by these monographs. The first purpose, whose fulfilment will probably render to chemists in general the most important service, is to present the knowledge available upon the chosen topic in a readable form, intelligible to those whose activities may be along a wholly different line. Many chemists fail to realize how closely their investigations may be connected with other work which on the surface appears far afield from their own. These monographs will enable such men to form closer contact with the work of chemists in other lines of research. The second purpose is to promote research in the branch of science covered by the monograph, by furnishing a well digested survey of the progress already made in that field and by pointing out directions in which investigation needs to be extended. To facilitate the attainment of this purpose, it is intended to include extended references to the literature, which will enable anyone interested to follow up the subject in more detail. If the literature is so voluminous that a complete bibliography is impracticable, a critical selection will be made of those papers which are most important.

The publication of these books marks a distinct departure in the policy of the American Chemical Society inasmuch as it is a serious attempt to found an American chemical literature without primary regard to commercial considerations. The success of the venture will depend in large part upon the measure of coöperation which can be secured in the preparation of books dealing adequately with topics of general interest; it is earnestly hoped, therefore, that every member of the various organizations in the chemical and allied industries will recognize the importance of the enterprise and take sufficient interest to justify it.

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TO MY
FATHER AND MOTHER
THIS BOOK IS
AFFECTIONATELY DEDICATED

Author's Preface

It is becoming increasingly evident that the application of physical science to the study of organic compounds is being amply repaid in that we can now more extensively base our knowledge of organic reactions on the laws of physical science rather than on empirical rules discovered in the laboratory. Indeed, it would seem that without the use of physical science, organic chemistry is likely to consist of the synthesis of new compounds of no paramount importance or to become an applied science, the handmaid of medicine or biology. Many of the problems of organic chemistry, a typical example being the Walden Inversion, appear to be insoluble by the old classical synthetic methods and such difficulties as this together with the newer discoveries in physical science have given a great impetus to its application in organic chemistry.

Fortunately the work that has been done so far from this point of view has proved extremely fruitful, in that whole new fields of investigation in organic chemistry have been opened up. Indeed, it seems quite probable that the advance of physical organic chemistry in this century may very well parallel the advance of organic chemistry in the last century. The application of thermodynamics to organic chemistry shows that it is possible in many cases to predict whether reactions will take place, without any laboratory work. The application of subatomics to organic chemistry, especially from the light absorption point of view, shows that we can tell far more about the shape and size of organic molecules than ever could be possible by the old classical methods. This enumerates only two of the many applications of physical science to organic chemistry.

Finally there is the application of reaction kinetics to the study of organic compounds which is the subject of this book. Reaction kinetics provides us with a powerful weapon for investigating the mechanism of organic reactions and has been freely used for this purpose in nearly all investigations concerning the mechanism of organic reactions. It therefore appeared desirable to make a systematic study of homogeneous organic reactions from this point of view so that the information available would be collected and presented in a more accessible form than scattered through the literature.

The author wishes to thank Dr. John R. Johnson of Cornell University for his very helpful suggestions and criticisms and Mr. R. N. Washburne of the Johns Hopkins University for much help with indexing and proof reading. The author is also greatly indebted to Professor W. A. Noyes, Editor of the Scientific Monographs of the American Chemical Society for much help and advice and to the Chemical Catalog Co. for cooperation in the later stages of the work.

F. O. RICE.

BALTIMORE, MARYLAND,
OCTOBER 15, 1927.

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THE MECHANISM OF HOMOGENEOUS ORGANIC REACTIONS

Chapter I.

Introduction.

A general study of reactions in homogeneous systems occurring at a rate slow enough to be measured will consist very largely of transformations and reactions of organic compounds under the influence of hydrogen or hydroxyl ions. A very large proportion of slow reactions contain an organic compound as one of the reactants; a very large proportion of these reactions are obviously affected by hydrogen or hydroxyl ions; it therefore seems to be not altogether outside the bounds of possibility that all slow reactions which are really homogeneous will fall into this class.

The non-reactivity of organic compounds when free from catalysts may be illustrated by ethylene and bromine which practically cease to react [1] when dry and enclosed by "non-polar" walls of paraffin wax. A great many other organic chemical reactions, such as the conversion of nitrocamphor to the pseudo form and the tautomerism of keto-enol isomers (*see* Chapter V), behave in the same manner when free from catalysts and enclosed in a vessel with non-polar walls.

The behavior of organic reactions between dissolved substances is in marked contrast to that of inorganic reactions; thus, an aqueous solution containing the thiosulfate ion and iodine react instantaneously, but if we replace the thiosulfate ion by an organic compound, such as acetone, or replace the iodine by an organic compound, such as methyl iodide, the resulting chemical reaction is very slow and takes many hours to reach equilibrium. If any appreciable proportion of inorganic reactions behaved in this manner, qualitative and quantitative analysis as we now know them would be impracticable. We must not conclude from this that most reactions between inorganic substances are non-catalytic, for

[1] Norrish, *J. Chem. Soc.*, **123**, 3006 (1923).

their behavior on extreme desiccation completely negatives this. Usually, however, such inorganic reactions are so extremely sensitive to minute traces of water that they occur instantaneously under ordinary conditions, so that the question as to whether or not they are catalytic becomes of slight practical interest.

As ordinarily performed, all reactions occur in presence of water; indeed, not only do solutions absorb water from the air, but they are also surrounded by a dilute aqueous solution of alkali which exists as a film on glass vessels. There are a number of organic reactions which are very sensitive catalytically, so that they are markedly affected by such traces of water or alkali. We must, therefore, be continually on guard to avoid treating as homogeneous, reactions which are catalyzed by the walls of the vessel, by dust particles in the solution or by precipitates which may form during the course of the reaction.

When studying a chemical reaction, the first and most important information which we should obtain is the free energy change and its variation with temperature; this information will tell us whether the proposed reaction is possible. In many cases, particularly in homogeneous inorganic solutions, this information is sufficient to describe the chemical behavior of the system completely. There are, however, many cases in which this information alone is of comparatively little use; for example, the oxidation of 1 mole of sulfur dioxide to sulfur trioxide liberates about 16,000 calories of free energy at ordinary temperatures, yet sulfur dioxide and oxygen do not combine spontaneously. This is the problem we meet continually in organic chemistry; in addition to the necessary thermodynamic information we must also have information about catalysts and reaction rates before we can describe a reaction completely.

The study of homogeneous catalysis in organic chemistry is very complicated. Since organic molecules are usually complex there is usually more than one way in which a molecule may break down or react, depending probably on the point of collision with the catalyst. Furthermore the resultants may be susceptible to catalytic influence and undergo further changes amongst themselves or with the reactants. Again, many organic reactions are carried out in solution, so that compound formation between solvent and reactants and resultants must be considered. Finally, the nature of the catalyst in homogeneous systems is still far from being understood. Originally the approximate proportionality between the catalytic activity of an acid and its degree of dissociation as determined by conductivity measurements led to the identification of the catalytically active particle as the ordinary hydrogen ion which is responsible

for electrolytic conduction. It soon became evident that this postulate was inadequate to account for experimental results (especially neutral salt action), and a second postulate was made, namely, that the undissociated acid molecule is catalytically active, sometimes two or three times as active as the hydrogen ion. A further development of this hypothesis is that the number of catalytically active particles is large and consists of the undissociated acid molecule and compounds of the hydrogen ion with the solvent and reactants and resultants. On this hypothesis, what appears to be a single reaction consists really of a large number of simultaneous reactions each proceeding at a rate determined by its particular catalyst.

It is evident therefore that when discussing the kinetics of an organic reaction most of our difficulties will be associated with the mechanism of the change. Falk [2] when discussing this problem states: "The three concepts, chemical reaction, chemical equation, and mathematical equation, are supposed to describe the same phenomenon in any given case. Actually they do so only as an ideal condition, and the possibility of deviation becomes greater with increasing complexity of the reactions and with decreasing care in the use of terms and expressions." Actually our stoichiometric equations hardly ever represent even approximately the reactions that take place in homogeneous solutions because they invariably neglect the possibility of compound formation between solvent and dissolved substances; also in these stoichiometric equations the existence of the catalyst is usually ignored, this being justified by some such manifest untruth as "The chemical nature of a catalyst is unchanged at the end of the reaction."

Evidently when discussing reaction mechanisms it is necessary always to take into account compound formation between solvent and dissolved substances; consequently the ordinary stoichiometric equations will only seldom be used, being replaced by equations which represent more nearly the reaction that actually occurs in the solution. The actual mechanism is nearly always much more complicated than one would suspect from the stoichiometric equation. When a substance A dissolves in a solvent, water for example, it is assumed that a simple binary compound $A.H_2O$ is formed, and we have the equilibrium,

$$A + H_2O \rightleftarrows A.H_2O,$$

which is probably attained instantaneously. If the substance A is very

[2] Falk, "The Chemistry of Enzyme Actions," Second Edition, p. 36. The Chemical Catalog Co.

soluble in water we may assume that it is largely hydrated and that the equilibrium concentration of A is small; if A is slightly soluble in water, the converse is assumed. The existence and treatment of these double compounds are dealt with much more fully in Chapter III.

With regard to the catalyst, it is assumed that in hydrogen-ion and hydroxyl-ion catalysis (which are by far the most important types in homogeneous organic chemistry) the unsolvated ions are the only catalytically active particles. The undissociated acid molecule and the various complexes of the hydrogen or hydroxyl ion are supposed to have no catalytic activity.

The mechanism of organic reactions in homogeneous solution is therefore pictured to be a rate of collision between dry hydrogen or hydroxyl ion and various solvated and unsolvated forms of the reactants. The intention of the author is to give a systematic account of homogeneous organic reactions from this point of view. It is implicitly assumed that there is no "natural rate" [3] and that in the absence of a catalyst the reaction does not occur. It seems probable also that the catalytic action ascribed to particular solvents is often only a secondary effect due not to the solvent directly but due to ionization and consequent activation of a catalyst when dissolved in the particular solvent. Sometimes, too, a solvent may contain accidental traces of impurities which are catalysts for a particular reaction.

When reading the literature of organic chemistry one often sees such statements as: "The two substances may be heated together in a sealed tube to give the product or better by heating together at ordinary pressures in presence of a catalyst." We feel that this statement really should read as follows: "The two substances combine when heated in a sealed tube owing to the accidental presence of slight traces of catalytic impurities and also possible catalysis by the walls of the tube; however, the reaction may be conducted in a much more satisfactory fashion by adding the necessary catalyst, when the substances combine readily at a much lower temperature and at ordinary pressures."

It must be noted that there is no mechanism of homogeneous catalysis upon which chemists are agreed; the above hypothesis has been adopted because it has the advantage of simplicity and may be used to explain qualitatively practically all organic reactions. Its use throughout

[3] Or that the "natural rate" is utterly negligible. For example, it might be suspected that two molecules possessing ten times the average speed and the proper orientation towards each other would react. This mechanism is of course quite different from the catalytic mechanism and it is assumed that such a reaction between molecules which have acquired a critical momentum is negligibly slow.

the book gives a unity which would be quite lacking if the many mutually exclusive views of different workers were used to explain reactions which are almost certainly basically similar. In all cases an earnest endeavor has been made to express fully the suggested mechanism by equations which represent, so far as we know, the actual reactions occurring in the solution. The relative speeds of the different reactions and the approximate equilibrium points are also indicated. It must be emphasized, however, that there is no "theory" of reaction rates in homogeneous systems; the best that can be offered in the present state of our science is a simple consistent explanation of the kinetics of organic reaction in accord with physical-chemical theory and observations.

A difficulty which has come up again and again in reviewing the subject of homogeneous catalysis is a report of the inexplicable behavior of some substance as a catalyst. In some cases this is simply the unconfirmed observation of a single worker, but sometimes the work has been repeated and found to be incorrect. For example Beckmann and Bark [4] studied the effect of heating benzophenone oxime with potassium chloride and reported that at 160° they obtained a mixture of about equal parts of benzanilide and unchanged oxime; on replacing the potassium chloride by sodium chloride they obtained no action, even when the temperature was increased to 250°, for the oxime was recovered unchanged. Lachman [5] repeated this work and concluded: "These data are entirely out of accord with the work described here. They must be the result of some errors of observation or manipulation for I have not been able to verify them. When mixtures of the oxime with sodium and with potassium chloride were heated side by side in the same bath, both behaved alike. There was a violent action at 185°; all of the oxime was converted into the mixture of ketone and imine already described, and no benzanilide was formed."

It is not a matter for discouragement that the mechanism of organic reactions is, in great part, so uncertain; even with the few tools now available a great many of the problems confronting us may be wholly or partly cleared up. Improvements in analytical technic which would enable us quickly and easily to estimate accurately the concentration of organic compounds present in a mixture would make possible a marked advance in the study of reaction kinetics. The development of some method of estimating the concentration of complex compounds present would probably have a similar effect. It does not seem likely, however,

[4] Beckman and Bark, *J. prakt. Chem.*, **105**, 327 (1923).
[5] Lachman, *J. Am. Chem. Soc.*, **46**, 1477 (1924).

that there will be any remarkable advance by proceeding along classical lines, and we may look for this only through the development of some new weapon comparable to the application of X-rays to the elucidation of problems of crystal structure. It is possible that the application of the newer theories of atomic structure may be the means of a general advance in the field of reaction mechanisms.

Chapter II.

Reaction Velocity.

Suppose we have a solution of 2 *M* aqueous cane sugar in presence of 1 *M* hydrochloric acid at 25°; the cane sugar hydrolyzes, and if we measure the concentration of cane sugar at definite time intervals we obtain a curve shown in Figure 1. The slope of the curve at any point

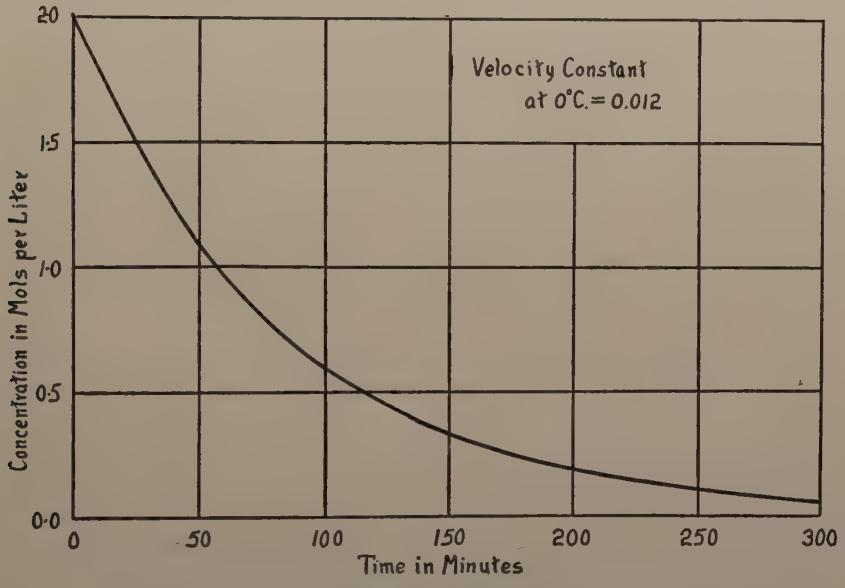


FIG. 1.—Hydrolysis of Aqueous Cane Sugar in Presence of 1 *M*. Hydrochloric Acid

gives the velocity of the reaction at that point, from which it is evident that the reaction starts with the highest velocity and falls gradually to zero; at a concentration of 2 *M* cane sugar the slope of the curve has the value 0.024 and at 1 *M* cane sugar the value 0.012. The slope of the curve or, what is the same thing, the rate of the reaction is therefore proportional to the concentration of cane sugar; this is the law of mass

action applied to chemical kinetics and is of fundamental importance since it is applied to all kinds of complicated reactions.

For ease of comparison of the rates of different reactions it is customary to give the rate of the reaction at a definite concentration; for example, in Figure 1 the tangent to the curve at 1 M cane sugar is 0.012, which means that 0.012 mole of sugar are hydrolyzed per minute in 1 liter of solution containing 1 mole of sugar and 1 mole of hydrochloric acid at 0°; this figure is known as the velocity constant of the reaction.[1] It is hardly ever convenient to measure reactions at such high concentrations. Usually the concentrations are between 0.01 M and 0.1 M, so that the velocity constant is not a measured figure but one calculated on the basis of the law of mass action. A complete statement of the velocity constant should therefore include the stoichiometric equation of the change and the actual concentrations of the reactants during the course of the measurement; this is necessary because very often the mass action law is not obeyed closely, so that the calculated value of the velocity constant will depend on the actual concentration of the reactants during the measurement. The temperature at which the reaction was measured should also be stated, since reaction rates nearly always vary rapidly with temperature. The method of calculating the velocity constant and stating the result may be illustrated by the hydrolysis of 0.5 M cane sugar by 0.2 M hydrochloric acid at 25°, since this gives a rate very convenient for measurement. Let a be the initial concentration of the hydrochloric acid which remains constant during the experiment, and b the initial concentration of the cane sugar; suppose x moles of cane sugar are hydrolyzed after t minutes. Applying the law of mass action, the rate of disappearance of cane sugar after t minutes is

$$-\frac{\mathrm{d}\,(b-x)}{\mathrm{d}t} \propto a(b-x).$$

This may be written

$$\frac{\mathrm{d}x}{\mathrm{d}t} = ka(b-x).$$

Integrating we obtain

$$k = \frac{1}{at} \ln \frac{b}{b-x}$$

The term $b/b-x$ is independent of the unit of concentration, so that we can replace it by polarimetric readings since these are very nearly additive. The term a, the concentration of hydrochloric acid, should be

[1] For another method of expressing the characteristic constant of a reaction see McBain, *Trans. Far. Soc.*, 13, 1 (1917); *Chem. News*, 116, 315 (1917).

expressed in moles per liter: t should be expressed in minutes. The velocity constant k will then be the number of moles of cane sugar hydrolyzed per minute in one liter of solution containing 1 M cane sugar and 1 M hydrochloric acid, the concentration of cane sugar being kept at its concentration of 1 M by some device such as the addition of sugar as fast as it is hydrolyzed. This of course is only a calculated figure and the importance of stating the actual concentrations of reactants may be seen from some results obtained [2] using different concentrations of catalyzing acid. The acid concentration was increased about twenty-five times and the calculated value for k was almost doubled (*see* Table I). The explanations offered for this variation will be considered in some detail later, but for the present it may be stated that stoichiometric equations hardly ever represent the true course of the reaction being measured. The function and state of the catalyst as well as double compound formation between reactants and solvent are usually ignored in stoichiometric equations but become all-important when considering reaction rates.

TABLE I

Hydrolysis of 0.3 M cane sugar by hydrochloric acid at 25°.

Normality of HCl	k
0.05	0.0084
0.25	0.0090
0.41	0.0098
0.90	0.0124
1.21	0.0144

Orders of Reactions

The different orders of reactions together with their equations will now be briefly discussed. Unimolecular reactions, or reactions of the first order, in which one molecule decomposes into one or more other molecules, are the simplest type but are of comparatively slight interest to the organic chemist because most of his reactions are catalytic and consequently are at least bimolecular. If a is the original concentration of substance and x moles per liter react in t minutes we have

$$-\frac{d(a-x)}{dt} = \frac{dx}{dt} = k_1(a-x).$$

Hence

$$k_1 = \frac{1}{t} ln \frac{a}{a-x},$$

[2] Lamble and Lewis, *J. Chem. Soc.*, 105, 233 (1915).

which is the characteristic equation of a unimolecular change. Probably the great majority of chemical reactions are bimolecular, and the complicated nature of many reactions is due merely to the simultaneous occurrence of two or more bimolecular reactions. There are very few examples of simple bimolecular reactions unaccompanied by others occurring at the same time. If a and b are the original concentrations of two substances A and B, and x moles per liter of A react after t minutes, we have

$$-\frac{d(a-x)}{dt} = \frac{dx}{dt} = k_2(a-x)(b-x).$$

Hence,

$$k_2 = \frac{1}{t(a-b)} ln \frac{b(a-x)}{a(b-x)}.$$

If two measurements be made at times t_1 and t_2 we have

$$k_2(a-b)(t_2-t_1) = ln \frac{a-x_2}{b-x_2} - ln \frac{a-x_1}{b-x_1}.$$

When a and b are near each other in value, these formulae are not satisfactory because any error in determining a or b becomes greatly magnified in the final result. By the use of infinite series [3] the objectionable $(a-b)$ term can be eliminated and we obtain

$$k_2 = \frac{1}{t}\frac{x}{ab} + \frac{a+b}{a^2b^2}\frac{x^2}{2} + \frac{a^2+ab+b^2}{a^3b^3}\frac{x^3}{3} + \frac{a^3+a^2b+ab^2+b^3}{a^4b^4}\frac{x^4}{4} + \cdots\cdots$$

If a and b are very near each other a further approximation may be made:

$$k_2 = \frac{1}{t}\frac{x}{ab} + \frac{a+b}{a^2b^2}\frac{x^2}{2} + \frac{x^3}{a^4} + \frac{x^4}{a^5} + \cdots\cdots$$

There are a number of special cases of bimolecular reactions such as when the substances A and B are present in equal concentration; the velocity equation then becomes

$$\frac{dx}{dt} = k_2(a-x)^2.$$

Integrating we obtain

$$k_2 = \frac{1}{t}\frac{x}{a(a-x)}.$$

If we make measurements at times t_1 and t_2 we may use the formula,

[3] See also Arrhenius, *Z. physik. Chem.*, 1, 115 (1887).

$$k_2(t_2 - t_1)a = \frac{x_2}{a - x_2} - \frac{x_1}{a - x_1},$$

where $(a-x_1)$ and $(a-x_2)$ are the concentrations of A at times t_1 and t_2 respectively. Another special case of bimolecular reactions occurs when the substance A is a catalyst whose concentration remains unchanged throughout the experiment, or when the concentration of A is greatly in excess of that of B; we have then

$$\frac{dx}{dt} = k_2 a(b - x).$$

Integration gives

$$k_2 = \frac{1}{at} ln \frac{b}{b - x}.$$

If we make measurements at t_1 and t_2 we have

$$k_2 = \frac{1}{a(t_2 - t_1)} \left[\frac{1}{b - x_2} - \frac{1}{b - x_1} \right].$$

Still another special case occurs when A is a catalyst and the reaction is autocatalytic producing one molecule of A for each molecule of A and B reacting. We then have

$$\frac{dx}{dt} = k_2(a + x)(b - x).$$

Integration gives

$$k_2 = \frac{1}{t(a + b)} ln \frac{b(a + x)}{a(b - x)}.$$

Trimolecular reactions are rare and only one or two special cases will be given. In a reaction between three substances A, B and C, the substance A may be a catalyst or be present in relatively high concentration compared to B and C. We have then

$$\frac{dx}{dt} = k_3 a(b - x)(c - x);$$

$$k_3 = \frac{1}{ta}(b - c)(c - a) ln \frac{c(b - x)}{b(c - x)}.$$

If A and B are both catalysts or if they are present in relatively high concentration compared with C we have

$$dx/dt = k_3 a b (c - x);$$

$$k_3 = \frac{1}{tab} ln \frac{c}{c - x}.$$

Simultaneous Reactions

So far we have dealt only with single isolated reactions; the study of organic chemistry even in spite of analytical difficulties would be comparatively simple if we had to deal only with isolated reactions. In actual practice, however, many complications occur, such as the products recombining to give a back reaction, the products reacting to form new substances giving consecutive reactions, and finally, the reactants combining in more than one way to give side reactions. Not only do we have these complications, but in many cases the reactants form double compounds with the solvent and often it is these complexes that react rather than the stoichiometric reactants; all these complications made the study of reaction rates somewhat difficult and the results often far from unequivocal. The difficulty is fundamentally an analytical one, namely, the quantitative estimation of the various substances at various times during the course of the reaction. We have no completely reliable method for demonstrating even the existence of complex compounds with the solvent, and convenient analytical methods for estimating the substances taking part in an organic reaction are only rarely available. The theoretical treatment of these reactions is quite simple and depends upon the principle that we can apply the law of mass action to each reaction independently of any other reactions occurring in the system at the same time.

Opposing Reactions

The simplest practical example which may be used to illustrate this is the conversion of a substance A under the influence of a catalyst C into a tautomeric substance B.

$$A + C \rightleftarrows B + C$$

After t minutes the velocity of the direct reaction is $k_1(a - x)c$ and the velocity of the reverse reaction is $k_2(b + x)c$ where a and b are the initial concentrations of A and B respectively, c is the constant concentration of catalyst and x is the number of moles of A per liter which change to the tautomeric form. The rate of the complete reaction is therefore given by,

$$-\frac{d(a-x)}{dt} = \frac{dx}{dt} = k_1(a-x)c - k_2(b+x)c.$$

Integration gives

$$k_1 + k_2 = \frac{1}{ct} ln \frac{k_1 a - k_2 b}{k_1 + k_2} - \frac{1}{ct} ln \left[\frac{k_1 a - k_2 b}{k_1 + k_2} - x\right].$$

We may obtain another relation between k_1 and k_2 by considering the equilibrium point when the velocities of the direct and reverse reaction are equal; x now has the special value x_e.

$$k_1(a - x_e) = k_2(b + x_e); \frac{b + x_e}{a - x_e} = \frac{k_1}{k_2} = K.$$

The two equations enable us to determine k_1 and k_2 separately.[4]

Consecutive Reactions

Next to opposing reactions perhaps the commonest type of reaction occurring in organic chemistry is consecutive reactions; the simplest case, and perhaps that most often met, is when one of the reactions is slow, the others being practically instantaneous. Double compound formation between reactants and solvent is probably the most frequent, especially in hydrolytic reactions. These reactions may be represented as occurring in two stages, the first being complex formation between reactant and solvent with very high velocity, and the second a slow breaking up of the complex by interaction with the catalyst. On these assumptions we may represent the hydrolysis of methyl acetate by hydrogen ions as follows:

$$CH_3COOCH_3 + H_2O \rightleftarrows CH_3COOCH_3.H_2O$$
$$CH_3COOCH_3.H_2O + H^+ \rightarrow CH_3COOH + CH_3OH + H^+.$$

If we assume that only a small fraction of the methyl acetate is hydrated, the concentration of the complex will be proportional to the total concentration of methyl acetate; hence the velocity of the reaction, while really determined by the concentration of the complex compound, appears to be determined directly by the methyl acetate. That some such complication is present is shown by results such as those of Ostwald,[5] who found that with the same acid concentration the value of the velocity constant changed from 19.9 to 24.2 as the initial concentration of methyl acetate changed from 0.27 *M* to 1.8 *M*. In the scheme suggested above it is assumed that the reaction involving complex compound formation is exceedingly rapid, so that the methyl acetate hydrate is always present at its equilibrium concentration; the collision of the methyl acetate hydrate with hydrogen ion is the slow reaction whose velocity is measured. This hydrolysis represents a very common type of reaction consisting of a fast reaction followed by a slow one; very often, unless the conditions

[4] Opposing reactions are discussed in the following papers: Küster, *Z. physik. Chem.*, 18, 171 (1895); Koelichen, *ibid.*, 33, 129 (1900); Trey, *ibid.*, 18, 198 (1895); Lowry, *J. Chem. Soc.*, 75, 227 (1899).

[5] Ostwald, *J. pr. Chem.*, 28, 449 (1883).

of the experiment are varied widely, the fast reactions escape notice altogether. Sometimes, however, an abnormality is immediately apparent as in the reaction between acetone and bromine [6] in aqueous solution, which is represented by

$$CH_3COCH_3 + Br_2 + H^+ = CH_3COCH_2Br + H^+ + HBr.$$

The rate of the reaction is proportional to the concentration of the acetone and the hydrogen ion but is quite independent of the concentration of the bromine. In this case we have to postulate that there is a slow reaction between acetone and hydrogen ion followed by an instantaneous bromination. Lapworth represents the action as enol formation:

$$CH_3COCH_3 + H^+ \rightleftarrows CH_3COH:CH_2 + H^+, \quad \text{Slow.}$$
$$CH_3COH:CH_2 + Br_2 = CH_3CBr(OH)\,CH_2Br, \quad \text{Fast.}$$
$$CH_3CBr(OH)CH_2Br = CH_3COCH_2Br + HBr. \quad \text{Fast.}$$

The more complicated case of successive reactions occurs when the rates of the different reactions are of nearly the same order of magnitude; the hydrolysis of the esters of polybasic acids provides the most commonly occurring examples of this. Wegscheider [7] gives an outline of the theoretical treatment of consecutive reactions with special reference to the formation and decomposition of esters of dicarboxylic acids; these reactions undoubtedly occur in at least two stages, since acid esters can be isolated from the mixture. Skrabal [8] also gives a theoretical discussion of these reactions together with a partial review of the literature.

The hydrolysis of dimethyl oxalate and the esterification of oxalic acid in aqueous methanol solution show that the first stage in each process occurs approximately twice as fast as the second.[9] The alkaline hydrolysis of esters of symmetrical homologs of oxalic acid yields somewhat similar results.[10] The hydrolysis of triacetin has been carefully investigated; [11] obviously such a reaction is very complex and unless some simplification could be introduced, its chemical kinetics would be almost hopelessly involved. However, in an investigation of different esters of the same acid de Hemptine and Löwenherz [12] found that the

[6] Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).
[7] Wegscheider, *Monatsh.*, **36**, 471 (1915).
[8] Skrabal, *Monatsh.*, **39**, 741 (1918); *idem, ibid.*, **37**, 137 (1916).
[9] See Skrabal and Mrazek, *Monatsh.*, **39**, 697 (1918).
[10] Skrabal and Singer, *Monatsh.*, **41**, 339 (1920).
[11] Meyer, *Z. Elektrochem.*, **13**, 186, 485 (1907); *idem, Z. physik. Chem.*, **66**, 87 (1908); *idem, ibid.*, **67**, 257 (1909); Yamasaki, *J. Am. Chem. Soc.*, **42**, 1455 (1920).
[12] de Hemptine, *Z. physik. Chem.*, **13**, 561 (1894); Löwenherz, *ibid.*, **15**, 389 (1894).

rate of hydrolysis is independent of the nature of the alcohol radicals; that is, esters of primary, secondary, and tertiary alcohols have the same velocity constant of hydrolysis when the acid is the same. It was found that this holds true in the case of the ester of a polyvalent alcohol such as glycerine, so that the kinetics of the triacetin hydrolysis is considerably simplified and the rates of hydrolysis are simply expressed in the same way as those of the successive reactions $M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow M_4$ which have, respectively, the velocity constants $3k$, $2k$ and k. The hydrolysis of triethyl citrate and the ethyl hydrogen citrates has been studied by Pinner,[13] and there are a number of other studies of consecutive reactions available.[14]

Side Reactions

The third complication which may occur in homogeneous reactions is the decomposition of the reactant in more than one way, giving rise to side reactions. The most commonly quoted example is the decomposition of hydroxylamine:[15]

$$3\,NH_2OH = NH_3 + N_2 + 3\,H_2O$$
$$4\,NH_2OH = 2\,NH_3 + N_2O + 3\,H_2O.$$

Suppose we have a substance A which under the influence of a catalyst C changes into two substances B and D; we have then

$$A + C = B; \qquad A + C = D.$$

The rate of the first reaction after t minutes is $k_1\,c(a-x)$ and the rate of the second reaction after t minutes is $k_2\,c(a-x)$, since the quantity $(a-x)$ is the concentration of A after t minutes. The sum of these gives us the total rate of change of A so that

$$\frac{dx}{dt} = k_1c(a-x) + k_2c(a-x) = c(a-x)(k_1+k_2).$$

Integrating we obtain,

$$k_1 + k_2 = \frac{1}{ct}\,ln\,\frac{a}{a-x}.$$

We obtain a second relation between k_1 and k_2 by noting that

$$\frac{\text{Rate of formation of } B \text{ at time } t}{\text{Rate of formation of } D \text{ at time } t} = \frac{k_1c(a-x)}{k_2c(a-x)} = \frac{k_1}{k_2} = \text{constant}.$$

[13] Pinner, *Z. Elektrochem.*, **24**, 21 (1918).
[14] See Herz and Kuntze, *Z. Elektrochem.*, **18**, 1015 (1912); Scheffer, *Rec. trav. chim.*, **40**, 477 (1921); Wegscheider, *Z. Elektrochem.*, **28**, 99 (1922); Smith, *Z. physik. Chem.*, **95**, 66 (1920).
[15] Tanatar, *Z. physik. Chem.*, **40**, 475 (1902).

Since this ratio of the rates is constant throughout the experiment we must have,

$$\frac{\text{Total amount of } B \text{ present at end}}{\text{Total amount of } D \text{ present at end}} = \frac{k_1}{k_2},$$

which gives us a means of measuring the velocity constant by simply measuring the concentration of A at definite time intervals and then measuring the ratio of the concentrations of B and D at the end of the experiment. This method holds only if the reactions are of the same order; if the reactions are not of the same order the concentrations of *two* of the substances must be determined at different time intervals.[16]

Analytical Procedure

The greatest difficulty in studying the kinetics of organic reactions lies in the analytical procedure; when one of the substances which changes in concentration is an acid or a base the technic is usually comparatively simple since the ordinary methods of acidimetry and alkalimetry can be used; similarly there are many organic reactions which involve an easily estimated substance such as a halogen which can be used to determine the rate of the reaction. For the great bulk of organic reactions, however, none of the reactants is readily estimated, and special methods must be devised to meet each case.

The most common of these special methods is the use of the polarimeter for optically active substances. By assuming (which is usually approximately correct) that optical rotations are additive we can obtain the $a/a - x$ term directly from polarimetric readings. This is so convenient that naturally this method has been used wherever possible [17] and in the case of sugar reactions an immense literature has grown up. Another optical method, also somewhat limited in scope, is change in color; Lapworth [18] studied the rate of addition of hydrocyanic acid to camphorquinone using this method. He states: "It was decided to resort to a method of investigation in which the speed of reaction could be roughly gaged by means of a color change, and for this purpose advantage was taken of the fact that camphorquinone has a bright yel-

[16] For the study of side reactions see, Wegscheider, *Z. physik. Chem.*, (a) **30**, 593 (1899); (b) **34**, 290 (1900).

[17] Cane sugar hydrolysis: Bibliography to 1906 by Caldwell, *Brit. Ass. Rep.*, 1906, p. 267; Mutarotation: Lowry, *J. Chem. Soc.*, **83**, 1314 (1903); *idem, ibid.*, **85**, 1551 (1904); Euler, Ölander and Rudberg, *Z. anorg. allgem. Chem.*, **146**, 45 (1925). Nitrocamphor: Lowry, *J. Chem. Soc.*, **93**, 107, 119 (1908). Menthone: Gruse and Acree, *J. Am. Chem. Soc.*, **39**, 376 (1917); Grossman and Brauer, *J. prakt. Chem.*, **98**, 9 (1918).

[18] Lapworth, *J. Chem. Soc.*, **83**, 995 (1903).

low color, which is perceptible even in very dilute solutions, while its cyanohydrin is almost if not quite colorless." This method could be developed to give accurate results by using a colorimeter which would permit accurate comparison of color intensities. The conversion of creatine into creatinine was studied by Edgar and Wakefield [19] using a colorimetric method [20] for estimating the creatinine formed; here the reaction was stopped and the creatinine determined colorimetrically.

The change in refractive index has also been used [21] to measure rate of chemical reaction; the rate of hydrolysis of cane sugar was measured by assuming that the specific refractive index is additive. No doubt this method could be made much more precise by applying interferometry, especially if monochromatic light were used, of wave length near that at which one of the constituents absorbs strongly. Indeed if the organic substance undergoing change absorbs light in the middle or long wave ultra-violet and if the absorption spectrum of the products differ appreciably from that of the original substance, simple refractometric measurements could be used for following accurately the course of the reaction. This depends upon the principle that the refractive index is greatly increased for lines on the long wave length side of an absorption band; in order to use this method it would be necessary to measure the change in refractive index during the course of a reaction for a wave length near the absorption band and on the long wave length side of it.

The change in volume or density of a solution as the reaction proceeds may also be used [22] to measure the rate of the reaction. Owing to the small change which occurs this method is not very accurate. A few reactions evolve gas [23] and the rate of evolution may be used to give a measure of the rate of the reaction; it should be noted that vigorous stirring is necessary [24] to obtain quantitative results. Frequently a reaction may be followed by a change in conductivity of the solution; Walker [25] has used conductivity measurements for measuring the rate of hydrolysis of esters by alkalis and has shown that the results agree with those

[19] Edgar and Wakefield, *J. Am. Chem. Soc.*, **45**, 2242 (1923).
[20] Folin, *Am. J. Physiol.*, **13**, 48 (1905).
[21] Duane, *Am. J. Sc.*, **11**, 349 (1901).
[22] Benrath, *Z. physik. Chem.*, **67**, 501 (1909); Anderson and Holden, *J. Phys. C.*, **18**, 152 (1914); Kolkatkar, *J. Chem. Soc.*, **107**, 921 (1915).
[23] See Francis and co-workers, *J. Chem. Soc.*, **101**, 2358 (1912); *ibid.*, **103**, 1722 (1913); *ibid.*, **107**, 1651 (1915); Fraenkel, *Z. physik. Chem.*, **60**, 202 (1907); Mumm, *ibid.*, **62**, 589 (1908); Millar, *ibid.*, **85**, 129 (1913); Braune, *ibid.*, **85**, 170 (1913); Cain, *J. Chem. Soc.*, (a) **81**, 1412 (1902); (b) **83**, 206, 470 (1903); Kilpatrick, *J. Am. Chem. Soc.*, **48**, 2091 (1926).
[24] Metschl, *J. Phys. Chem.*, **28**, 417 (1924); Findlay and co-workers, *J. Chem. Soc.*, (a) **103**, 1170 (1914); (b) **105**, 1297 (1914); (c) **121**, 1046 (1922).
[25] Walker, *Proc. Roy. Soc.*, **78A**, 157 (1906).

obtained by other methods. He states: "The chief conditions for the convenient application of the method are, first, that there should be a considerable difference in conductivity between the initial and final systems, and second, that the change in conductivity should be proportional to the progress of the reaction. It occurred to me that these conditions would be well fulfilled in the saponification of an ester by a caustic alkali. The conductivity of the alkali, say sodium hydroxide, is much greater than that of the sodium salt produced by the saponification, owing to the high velocity of hydroxyl ion as compared with the salt anion. Since, too, sodium hydroxide and sodium salts of monobasic acids are approximately equally ionized under the same conditions, the ionization in dilute solution remains practically the same throughout the saponification, and thus the alteration in the conductivity is almost exactly proportional to the progress of the reaction." The method has been used for measuring the rate of reaction between methyl sulfate [26] and methanol as well as in a number of other reactions.[27]

For the bulk of organic reactions, however, none of these methods is available, and special methods have to be devised depending on the particular experiment. For example the rearrangement of potassium dibenzhydroxamate to diphenyl urea was studied [28] by acidifying portions of the solution at definite time intervals and estimating the free dibenzhydroxamic acid gravimetrically. Freundlich and Pape [29] measured the rates of some reactions by the rate of coagulation of arsenious sulfide sols.

Errors of Measurement

The errors in measuring reaction rates [30] may now be discussed. The commonest error affecting the constancy of k is a lack of knowledge of the true mechanism of the reactions; the presence of secondary reactions in addition to the main reaction will usually cause a drift in the constant which can be eliminated only by studying the other reactions and correcting for them. Another error is partial loss of one of the reactants through volatility; this loss is nearly always appreciable because of the common method of making up the reacting solution and

[26] Centnerzwer, *Z. physik. Chem. Unterr.*, **26**. 344 (1914).
[27] Walker and Kay, *J. Chem. Soc.*, **71**, 489 (1897); Cohen and Kaiser, *Z. physik. Chem.*, **89**, 357 (1915).
[28] Dougherty and Jones, *J. Am. Chem. Soc.*, **46**, 1535 (1924).
[29] Freundlich and Pape, *Z. physik. Chem.*, **86**, 458 (1914).
[30] Moesveld, *Z. physik. Chem.*, **103**, 481 (1923); Wagner, *ibid.*, **115**, 130 (1925); Rice and Kilpatrick, *J. Am. Chem. Soc.*, **45**, 1361 (1923); Rice, Fryling and Wesolowski, *ibid.*, **46**, 2405 (1924); Gerasimov, *J. Russ. Phys. Chem. Soc.*, **48**, 456 (1916).

then opening the vessel some six to twelve times to withdraw samples for analysis. The best way to avoid this error is to make up the solution and then siphon it into a series of smaller vessels, filling each one; by keeping the various vessels in the thermostat or by working rapidly outside of the thermostat this operation may be done while the reaction is going, without appreciable error; the contents of the small vessels may then be analyzed at convenient time intervals. A third source of error arises from the use of the logarithmic formulas for calculating k; in the early stages of the reaction the value of the quantities inside the logarithmic term are only slightly greater than 1 and under these conditions a slight change in the number causes a very large change in the value of the logarithm; consequently small analytical errors become greatly magnified in the final results. Again, at the end of the reaction the reactants are at small concentrations and the analytical error becomes correspondingly great. It is evident therefore that observations taken near the beginning or near the end of a reaction have relatively little value, and it seems desirable to modify the standard procedure by making only one or two titrations near the point at which the errors in the direct measurements have least effect on the result. Opening the reaction vessel at other points to withdraw samples adds but little to the precision of the final result and introduces large errors if the solution contains volatile reactants. An investigation [81] showed that these errors have a minimum value when the reaction has proceeded a little over half way; consequently it would appear most desirable to make simply one or two titrations at this point and then repeat the experiment, using different initial concentrations of the reactants. Finally, the temperature must be carefully controlled since reaction rates usually vary rapidly with temperature.

Reaction Velocity and Temperature

The relation between reaction velocity and temperature is usually expressed in the form of an empirical equation first used by Arrhenius:

$$\frac{1}{k}\frac{dk}{dT} = \frac{Q}{RT^2} \text{ or } \frac{d\,ln\,k}{dT} = \frac{Q}{RT^2},$$

where Q is a constant and R is the gas constant. $1/k.dk/dT$ is the temperature coefficient of the reaction, i.e., the increase of the velocity per unit velocity per degree rise in temperature; the temperature coefficient therefore diminishes rapidly with rise in temperature. The custom among chemists is to call the ratio of the velocities at two temperatures

[81] Rice, Fryling and Wesolowski, *J. Am. Soc.*, **46**, 2405 (1924).

10° apart, the temperature coefficient; usually 35° and 25° are selected, so that k_{35}/k_{25} is ordinarily termed the temperature coefficient. For these two temperatures the integrated form of the Arrhenius equation becomes,

$$2.303 \log \frac{k_{35}}{k_{25}} = \frac{Q}{1.986}\left(\frac{1}{298.1} - \frac{1}{308.1}\right), \text{ or } \log \frac{k_{35}}{k_{25}} = \frac{Q}{42{,}011}.$$

The variation in Q for different reactions is not very great, the limits being about 11,000 for the alkaline hydrolysis of esters and 26,000 for the acid hydrolysis of sugars; the corresponding values of k_{35}/k_{25} are 1.8 and 4.1 respectively.

The temperature coefficient of a reaction is a very important quantity and should always be measured; this can be done by measuring the velocity at two temperatures, or more conveniently and accurately by a method [32] in which the initial solution is divided into two parts, one of which is placed in one thermostat at 25° for example, and the other in another thermostat at 30°. The same reaction (except for certain small corrections) is then going at two temperatures, in this case 5° apart, and the temperature coefficient is therefore readily calculated. When using this method it is desirable to make a rough determination of the temperature coefficient and from this knowledge compare the rates at times when the two reactions have proceeded approximately to the same extent; highly accurate results may thus be obtained.

Mechanism of Organic Reactions

One of the most important methods of studying the mechanism of organic reactions is through rate measurements, and very often the results of such studies show that the ordinary stoichiometric equation by no means represents the true course of the reaction. The problem of determining the true mechanism of the reaction from the observations made is often one of great difficulty. This is largely due to the limitations of our analytical technic, for if we were able to estimate easily the concentrations of all the reactants and resultants, the problem would be comparatively simple. Usually, however, we can conveniently estimate only one of the reacting substances; but from our knowledge of the stoichiometric equation we can construct one or more equations more nearly representing the course of the reaction and from these we can calculate the concentrations of the various reactants at different time intervals. If there are no appreciable complications due to back reactions or side reactions or consecutive reactions we may then substitute

[32] Rice and Fryling, *J. Am. Chem. Soc.*, 47, 379 (1925).

the results in the different velocity equations and obtain the order of the reaction.

A modification of this method has been proposed by Ostwald [33] which is especially useful if we can conveniently estimate one of the products of the reaction. In this method all the reactants save one are present in relatively high concentration, and may be regarded as constant during the course of the reaction; the rate of appearance of the products of the reaction in any one experiment will therefore depend only on the reactant present in small concentration and measurements will show how many molecules of this reactant are taking part; the experiment is then repeated keeping another reactant in relatively low concentration; in this way the number of molecules of each substance reacting is determined and hence the order of the complete reaction. Unfortunately comparatively few reactions are sufficiently free from complications so that these methods are applicable. If the reaction is complicated only by a back reaction or a consecutive reaction we may confine the measurements to the early stages, when the effect of these complications is comparatively slight; this has the drawback that the work must be done extremely carefully, because any errors in the direct measurements for the early parts of the reactions are greatly multiplied in the velocity equation which gives the value of k, the velocity constant.

The method of van't Hoff [34] may also be used in this connection; it is based on the fact that the time taken to decompose some fractional part of the reactants is proportional to $1/a^{n-1}$, where a is the initial concentration and n is the order of the reaction. If we perform two experiments using different initial concentrations and measure the time of say one-fifth change we can determine n, the order of the reaction. The complete study of complicated reactions is greatly hampered by the analytical difficulty of estimating the various products of the change. If we could follow each substance analytically the whole treatment would be very simple, but unfortunately it is usually possible to analyze for only a few of the substances. The algebraic expressions often become very complicated and unless care is taken to analyze these from the point of view of precision of measurement, the results may be very misleading.

The study of reaction mechanisms from the point of view of velocity of reaction indicates that there is another factor apart from the ordinary stoichiometric complications which can profoundly modify the mechan-

[33] Ostwald, "Lehrbuch," 2, ii, 238 (1902).
[34] van't Hoff, "Etudes," 87, 1884.

ism of a reaction. This is the formation of complex compounds between the reactants and the solvent, and between the catalyst and the solvent. This becomes apparent when we take an apparently simple reaction and determine the rate over a wide range of concentration; even when we correct for the back reaction or other simultaneous change, the velocity constant shows a gradual change with the concentration of reactants. This variation will be discussed in some detail in connection with certain reactions [35] but it does not seem likely that the problem will be solved until some independent method is devised for estimating the concentrations of the various complex compounds in the solution.

Summary

A summary may be given to include the various special cases of reaction mechanisms; in all the equations given a, b, c, ..., are the initial concentrations in moles per liter of the reactants A, B, C,....., and n represents the number of moles of A per liter which react in t minutes.

(1) Unimolecular reactions. $A = B + C + ...$

$$-\frac{d(a-x)}{dt} = k_1(a-x)\,;\; k_1 = \frac{1}{t}\,ln\,\frac{a}{a-x}.$$

(2) Bimolecular reactions. $A + B = C + D + ...$

$$\frac{dx}{dt} = k_2\,(a-x)\,(b-x)\,;\; k_2 = \frac{1}{t(a-b)}\,ln\,\frac{b(a-x)}{a(b-x)}$$

$$k_2(a-b)\,(t_2-t_1) = ln\,\frac{a-x_2}{b-x_2} - ln\,\frac{a-x_1}{b-x_1}.$$

(a) When the initial concentrations of A and B are equal, we have:

$$\frac{dx}{dt} = k_2(a-x)^2\,;\; k_2 = \frac{1}{t}\,\frac{x}{a(a-x)}.$$

$$k_2\,(t_2-t_1)\,a = \frac{x_2}{a-x_2} - \frac{x_1}{a-x_1}.$$

(b) When the substance A is a catalyst or when its concentration is more than ten times that of B, we have:

$$\frac{dx}{dt} = k_2\,a(b-x)\,; \qquad k_2 = \frac{1}{at}\,ln\,\frac{b}{b-x}.$$

$$k_2 = \frac{1}{a(t_2-t_1)}\left[\frac{1}{b-x_2} - \frac{1}{b-x_1}\right].$$

[35] *See* Chapter VI.

(c) When the reaction is autocatalytic, $A + B = C + 2A$, we have:

$$\frac{dx}{dt} = k_2(a + x)(b - x)\,;\, k_2 = \frac{1}{t(a+b)}\, ln\, \frac{b(a+x)}{a(b-x)}.$$

(3) Trimolecular reactions.

(a) When the substance A is a catalyst or is present in relatively high concentration compared to B and C we have:

$$\frac{dx}{dt} = k_3\, a(b - x)(c - x)\,;\, k_3 = \frac{1}{ta}\,(b - c)(c - a)\, ln\, \frac{c(b-x)}{b(c-x)}.$$

(b) If A and B are both catalysts or if they are present in relatively high concentration compared to C we have:

$$\frac{dx}{dt} = k_3\, a\, b(c - x)\,;\, k_3 = \frac{1}{t\, a\, b}\, ln\, \frac{c}{c-x}.$$

Chapter III.

Addition Compound Formation.

Since the study of homogeneous catalysis comprises mainly the study of reaction rates of compounds in solution, it becomes important to consider the possible formation of complex compounds between the reactants and solvent, since the actual reaction which we measure may not be between the stoichiometric reactants but between addition products of these with the solvent. Probably most of our difficulties when discussing reaction mechanisms arise from this complication. It may be said at the outset that we have no completely unequivocal method for establishing even the existence of definite compounds in solution between solute and solvent; in consequence, there is something to be said for the old Ostwald-van't Hoff conception, in which the solute is supposed to behave as if alone and in the gaseous state.

Existence of Addition Compounds

The existence of hydrated ions in solution is now universally admitted, since a large amount of confirmatory evidence is in existence; it must be admitted, however, that most of this is circumstantial in character. Such evidence as that obtained by Washburn [1] is fairly convincing; if ions are hydrated, not only the electrolyte but also some of the water should be transferred from one electrode to the other during electrolysis. Washburn showed that this transfer of water could be made apparent when the solution contained a small quantity of a non-electrolyte which would not migrate with the current and which would be increased in concentration at one electrode and decreased at the other, as a result of the water transference.

Perhaps the most convincing evidence for the extensive hydration of dissolved ions is to be found in the work of Born and Fajans [2] on the heats of hydration of gaseous ions. These heats are very large, usually

[1] Washburn, *J. Am. Chem. Soc.*, **31**, 322 (1909).

[2] Born, *Ber. physik. Ges.*, **21**, 679 (1919); Fajans, *ibid.*, **21**, 649 (1919). A résumé of this work is given by Taylor, "Newer Aspects of Ionization Problems," *Trans. Am. Electrochem. Soc.*, **43**, 31 (1923). See also Webb, *J. Am. Chem. Soc.*, **48**, 2589 (1926).

between one and two hundred thousands calories per gram atom, so that it appears probable that dissolved ions are extensively hydrated. Fajans, however, considers that an ion does not form hydrates of definite stoichiometric composition; its solution in water is accompanied by an orientation of the water molecules in its immediate vicinity so that the oppositely charged parts of the water molecules are next to the ion; this envelope of orientated water molecules affects another layer and so on. It would seem that we may properly regard only the hydrogen ion as being capable of forming a hydrate of definite stoichiometric composition and that this hydrate must have the formula $(H_3O)^+$.

The evidence for the existence of compounds between non-polar substances in solution is not so satisfactory, as may be seen from a quotation from a recent paper:[3] "The classical method for establishing the presence of compounds in a solution (introduced by Mendelejeff and still in favor among the followers of his hydrate theory) consists in plotting some physical property of the mixture against its composition and noting the position of discontinuities either in the curve itself or in some derived function. No doubt this procedure will ultimately prove of value as our knowledge of solutions progresses, but the ludicrous and conflicting conclusions drawn from certain aqueous systems have succeeded not only in discrediting the method but also in creating the belief that compound formation in the liquid state is, even if sometimes an existent, yet in general an unimportant factor. For example, the failure of the Ostwald dilution law for strong electrolytes in aqueous solution has been referred to a great variety of causes, but rarely have the consequences of the solvent entering into the reaction in any way been seriously considered. Where such a possibility is mentioned, it is usually followed directly by the statement that, in dilute solutions at any rate, the effect upon the dissociation equilibrium of the solute will be negligible." However, a great many so-called non-polar molecules are in reality electric dipoles so that we may properly expect molecular association in such cases; for example in liquid water we should have complexes consisting of two, three, or more single water molecules.

Measurement of Compound Formation

Perhaps the best evidence for the existence of compounds in solution is obtained from freezing-point measurements.[4] If we add to a pure substance *A* a second pure substance *B*, the freezing-point of *A* is

[3] Kendall and Booge, *J. Am. Chem. Soc.*, 39, 2323 (1917).

[4] See Taylor, "Treatise on Physical Chemistry," D. Van Nostrand Co., New York, 1925, vol. I, p. 420.

lowered; similarly, the addition of A lowers the freezing-point of B. Plotting temperature against concentration gives two curves which intersect at the eutectic point. If, however, a compound $A.B$ is formed, this also acts as a pure substance, and its freezing-point is lowered by addition of either A or B; hence the freezing-point curve exhibits, in this case, a maximum, the position of the maximum on the axis of molecular concentration indicating the composition of the compound. A series of compounds is indicated by a series of maxima on the curve.

The great advantage of this method is that it is possible to read directly the composition of the compound on the concentration axis without isolating or analyzing it. It is also possible to judge very approximately the amount of double compound formation from the shape of the curve at the maximum point. A sharp maximum, i.e., a rapid decrease in the temperature of fusion of the compound on addition of either component, indicates extensive compound formation in solution; on the other hand, a flat maximum indicates a high degree of dissociation of the double compound at its melting-point as expressed by the equation

$$A + B \rightleftarrows A.B.$$

The equilibrium constant K of the reaction is given by

$$K = A.B/A \times B,$$

and if the compound $A.B$ is largely dissociated, the constant K of the reaction will be small. The extent of compound formation will be greatest when the concentrations of A and B are equal.

The chief drawback to the method is that it is limited to a special characteristic temperature for each pair of compounds investigated. It seems to be a general rule [5] that addition compounds are more stable the lower the temperature; i.e., in general, addition compound formation is an exothermic process, so that curves obtained at different temperatures are not strictly comparable. However, the heat change is usually small and it is still possible to use the curves as a basis for rough comparison if the temperatures are not too far apart. The method may be illustrated [6] by a series of compounds between trichloroacetic acid and various esters (Table II). It gives, however, only an approximate indication of the relative stability of compounds of different esters with trichloroacetic acid for two reasons, first, the comparisons are not made at the same temperature, and second, the heat of fusion of the complex should be considered since this heat is related to the freezing-point low-

[5] Kendall, *J. Am. Chem. Soc.*, **36**, 1722 (1914).
[6] Kendall and Booge, *J. Am. Chem. Soc.*, **38**, 1712 (1916).

ering. However, in spite of these drawbacks the method is of value in affording qualitative relationships.

TABLE II

System, Trichloroacetic Acid—Ester

Ester	Melting-Point of 1:1 Compound °C	Depression of Freezing-Point by Change of 5% from Maximum * °C
Ethyl acetate	—27.5	1.5
α-Naphthyl acetate	10.7	0.9
β-Naphthyl acetate	66.3	0.8
Ethyl benzoate	—23.4	1.2
Methyl benzoate	— 8.8	1.1
Benzyl benzoate	11.9	0.9
Methyl anisate	— 6.3	0.9
Methyl cinnamate	8.5	1.5

* Depression resulting from changing ester content of compound from 50 per cent to 45 per cent or 55 per cent.

Addition compounds may be formed in the liquid phase and yet not be induced to crystallize out, especially if the degree of dissociation into the components at the melting-point is large. In such cases, however, the extent of compound formation can be deduced from the change in slope of the freezing-point curve of either component. This gives a more general method of detecting compound formation than the actual isolation of the products. Kendall and Booge (*loc. cit.*) give a theoretical discussion of this method, which may be used by observing the freezing-point depression of a fixed substance *A* on addition of fixed molar fractions of different substances. These deviations from the ideal depression afford a legitimate basis for a strict comparison of compound stability which is independent of all special factors such as melting-point or heat of fusion of the compound. The method may be illustrated by the results shown in Figure 2; various esters were added to trichloroacetic acid and the freezing-point depressions of the acid measured; the upper curve shows the system trichloroacetic acid-benzene which probably approximates the ideal curve, since the substances show no sign of compound formation.

From Figure 2 we may conclude that the extent of addition compound formation of the esters with trichloroacetic acid is as follows: diethyl succinate > dimethyl succinate > dimethyl malonate > diethyl oxalate > dimethyl oxalate.

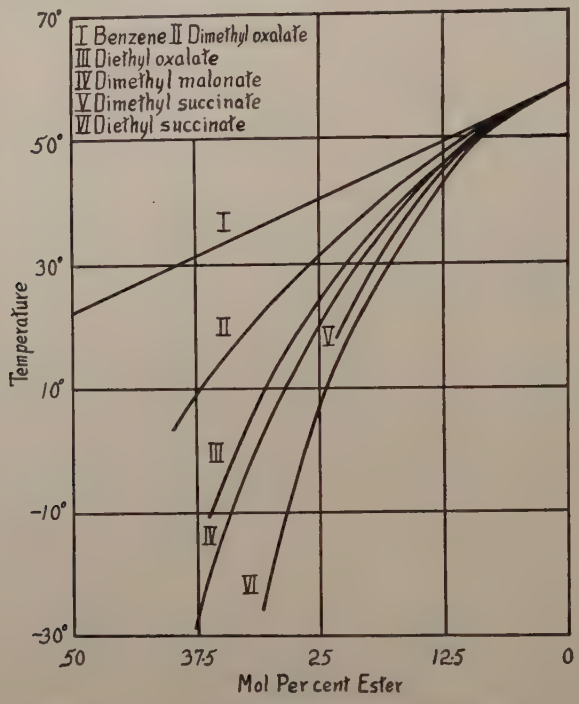
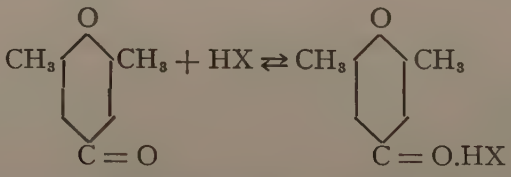


FIG. 2.—Systems: Trichloroacetic Acid—Ester.

Chemical Constitution and Addition Compound Formation

Kendall and his co-workers have made a series of studies [7] of addition compound formation of organic substances and the results enable us to predict when compound formation will take place and (approximately) to what extent. Dimethyl pyrone combines with acids, the : CO group having apparently pronounced basic characteristics:



[7] Dimethyl Pyrone and Organic Acids, Kendall, *J. Am. Chem. Soc.*, **36**, 1222 (1914); Organic Acids in Pairs, *idem, ibid.*, **36**, 1722 (1914); Organic Substances and Sulfuric Acid, Kendall and Carpenter, *ibid.*, **36**, 2498 (1914); Organic Acids with Aldehydes and Ketones, Kendall and Gibbons. *ibid.*, **37**, 149 (1915); Organic Acids and Phenols, Kendall, *ibid.*, **38**, 1309 (1916); Organic Acids and Esters, Kendall and Booge, *ibid.*, **38**, 1712 (1916).

The extent of combination depends upon the strength of the acid, i.e., on the negative character of the radical X (Fig. 3).

Altogether 32 organic acids were examined and 37 addition compounds were obtained; most of these were 1:1 compounds but a few compounds of the type $>C:O.2HX$ and $>C:O.3HX$ were obtained. Similar results were obtained for systems containing two organic acids (Fig. 4), but the form of the curves here showed that the compounds

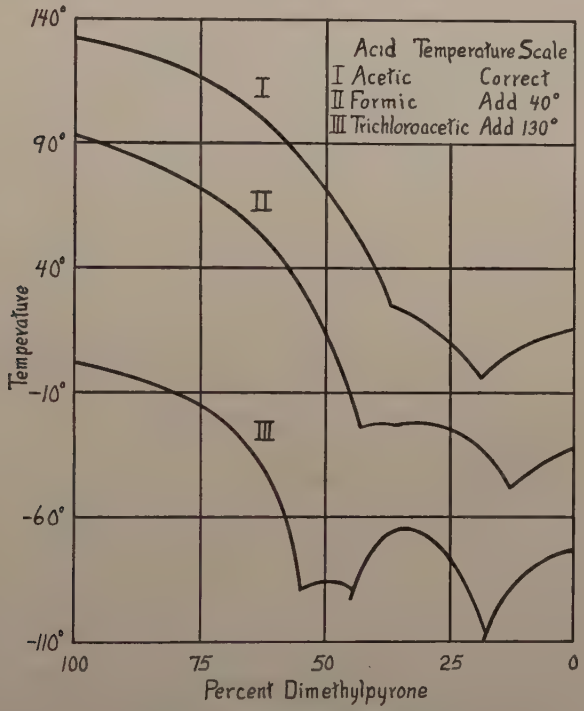


FIG. 3.—Systems: Dimethylpyrone—Organic Acid.

were much less stable than those with dimethyl pyrone. Systems consisting of weak organic acid-trichloroacetic acid yielded insolable addition compounds in five out of eight cases, systems consisting of weak organic acid-dichloroacetic acid yielded isolable compounds in two out of eight cases and systems consisting of weak organic acid-chloroacetic acid gave no isolable compounds. A study of systems consisting of 100 per cent sulfuric acid-organic compound gave very interesting results, since under the conditions of the experiment sulfonation only rarely took place.

The organic compounds used were aromatic and aliphatic acids, phenols, aldehydes and ketones. Most of the substances (Figs. 5 and 6) gave indications of compound formation, in many cases stable isolable compounds being obtained. Everywhere the rule is followed that the extent of compound formation depends upon the degree of diversity of the two

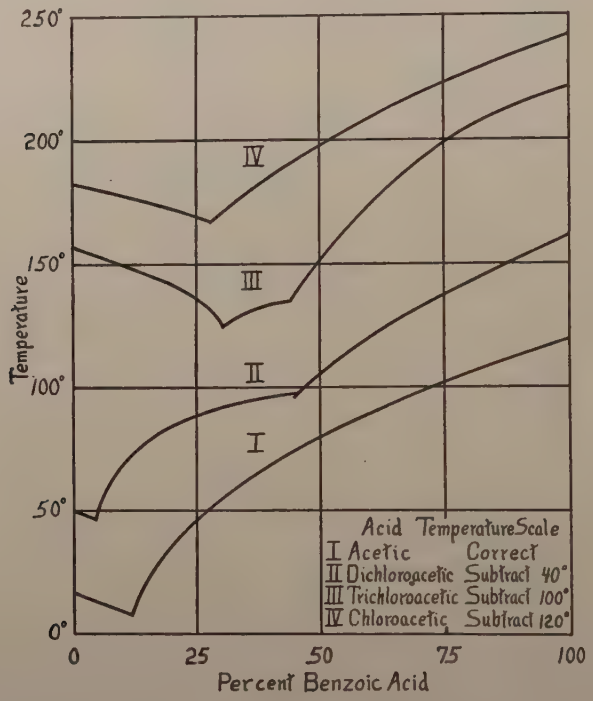


FIG. 4.—Systems: Weak Organic Acid—Strong Organic Acid.

components; compounds like dimethyl pyrone and other ketones and aldehydes, in which the $>C:O$ group may be regarded as having "basic characteristics," readily form stable complexes with strong acids, but do not combine readily with weak acids. Weak organic acids and phenols combine with strong acids. We never find weakly acidic substances combining with other weakly acidic substances or strong acids with strong acids; acetic acid and benzoic acid or phenol and *p*-cresol show no appreciable trace of compound formation. The stability of an addition compound increases with the differences in the character of its two components; further evidence for this is shown by compounds between

organic acids and phenols, some examples of these being shown in Figure 7. The final study of these addition compounds comprised systems of organic acids and esters, the results (Fig. 8) being in complete agreement with the rule just given: the esters of the stronger acids combine less than esters of the weaker acids and an ethyl ester shows more combination than the corresponding methyl ester, the ethyl radical being somewhat more positive than the methyl radical.

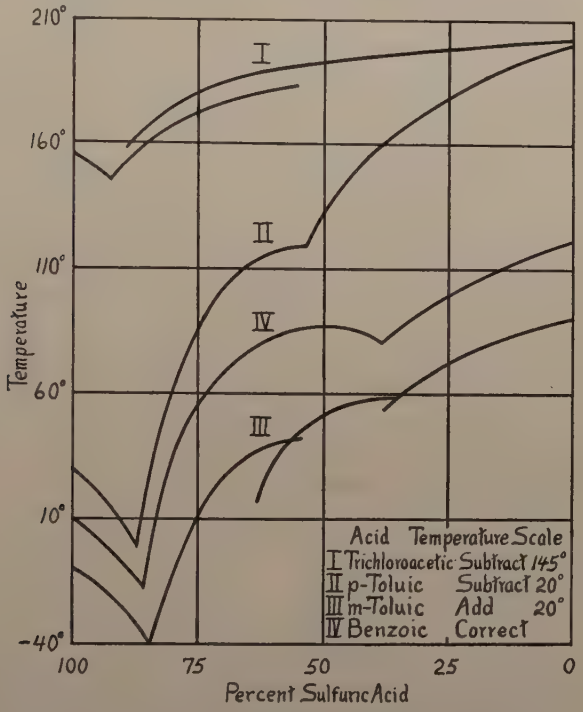
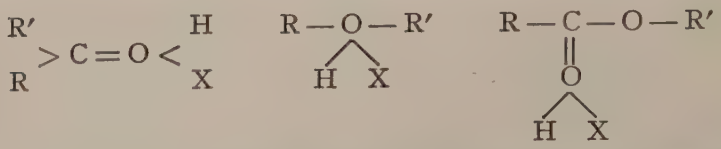


FIG. 5.—Systems: Sulfuric Acid—Organic Acid.

We may therefore summarize by saying that when an organic substance containing oxygen is added to an acid the existence of an addition compound in the liquid mixture can always be predicted, the evidence indicating oxonium salt formation:

$$\begin{matrix} R' \\ \\ R \end{matrix} > CO \qquad R-O-R' \qquad R-\underset{\underset{O}{\|}}{C}-O-R'$$



In the majority of cases combination is extensive and the conditions necessary for the actual isolation of the compound can be readily derived from the freezing-point curve of the system. The stability of the com-

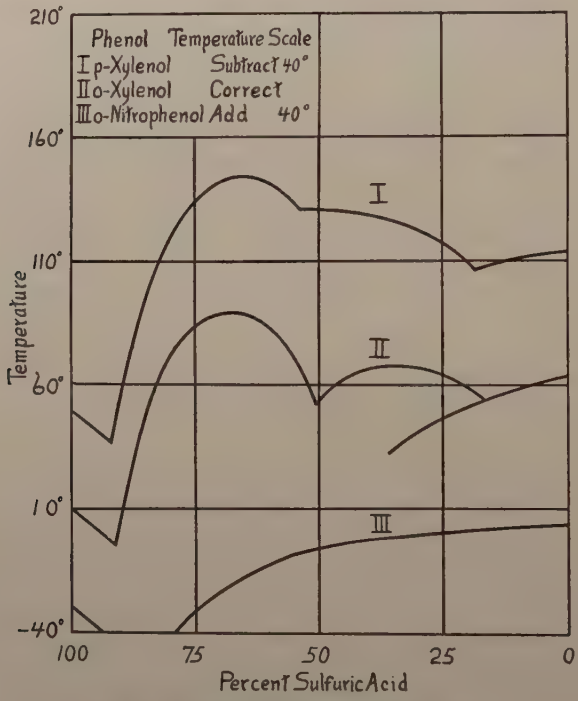


FIG. 6.—Systems: Sulfuric Acid—Phenol.

pound (or the degree to which its components exist in combination in the liquid state) can also be deduced from the sharpness of its maximum on this curve. We find that increase in the strength of the acid (i.e., in the negative character of the radical X) increases the stability of the compound; trichloroacetic acid gives stable addition compounds with nearly all of these oxygen-containing organic substances, but monochloroacetic acid rarely gives stable compounds. We also find that increase in the basic characteristics of the organic substance (i.e., in the positive nature of

the radicals R and R′) also increases the extent of compound formation. Thus trichloroacetic acid combines more firmly with ethyl acetate than with methyl benzoate, while its compound with benzyl benzoate is not sufficiently stable to be isolated.

These rules may be comprised in the statement that the stability of an addition compound increases with the differences in the character of its two components. Thus substances of similar acidic strengths such as

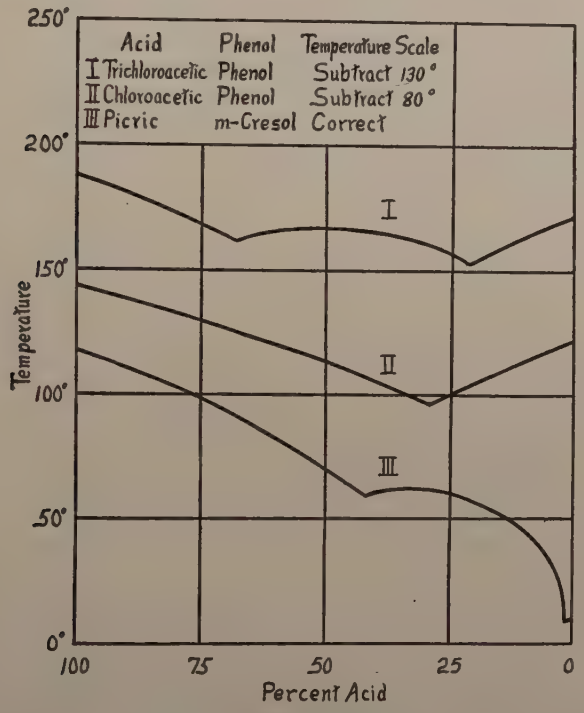


FIG. 7.—Systems: Organic Acid—Phenol.

acetic acid and benzoic acid or phenol and *o*-cresol exhibit no appreciable trace of compound formation; but if we substitute for the acetic acid, trichloroacetic aid or for the phenol, trinitrophenol, we greatly increase the acidic strength of one of the components and we get equimolecular compounds formed in each case.

Even when no compound can actually be isolated there may exist some compound formation in the liquid mixture. The extent of this may be judged by observing the freezing-point depressions when fixed

molecular fractions of a substance A are added to substance B; the derivations from the ideal depression curve give a basis for comparison of compound formation. The same rules are found to be valid in these cases also; thus in systems of the type CCl_3COOH — $RCOOR'$, the degree of combination varies with the ester as follows:

$$C_6H_4OHCOOC_6H_5 > C_6H_5COOC_6H_5 > C_6H_5COOCH_2C_6H_5 > C_6H_5COOCH_3 > C_6H_5COOC_2H_5 > CH_3COOC_2H_5.$$

Weaker acids give with the same esters much less stable compounds throughout. With uni-univalent components equimolecular compounds

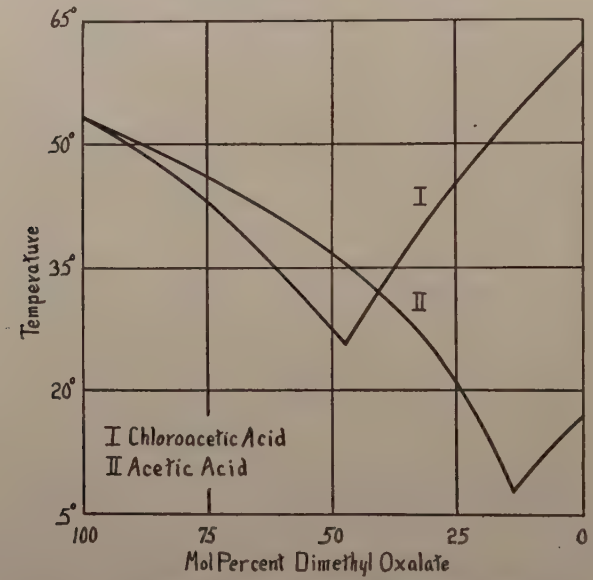


FIG. 8.—System : Organic Acid—Dimethyl Oxalate.

are the rule and more complex addition compounds appear only when the differences in character of the components are extreme.

We may now consider [8] the factor affecting the formation and stability of the systems, water—acid and water—base; with the system water —acid the conditions are exactly analogous to those for acids in pairs, the water functioning as a very weak acid. We should expect then to have no hydrate formation with very weak acids, and a regular increase in the extent of combination in the liquid state as the strength of the acid is increased. The transition and strong acids should give extensive com-

[8] Kendall, Booge and Andrews, *J. Am. Chem. Soc.*, 39, 2303 (1917).

pound formation and the isolation of stable hydrates in the solid state should now be possible; and increase in the complexity of the hydrates may now also be expected. These predictions are fulfilled with very few exceptions; thus neither weak organic acids [9] nor weak inorganic acids give isolable hydrates, whereas transition and strong acids both organic and inorganic afford numerous instances of hydrate formation. It seems a reasonable inference that strong acids must be largely combined with water when in solution, otherwise their hydrates could not separate out from the liquid phase; on the other hand weak acids cannot be combined with the solvent to any appreciable extent or some hydrates would certainly be known. A study of systems consisting of organic acid—water showed that the deviation from the ideal curve (which indicates the extent of compound formation) increases as the strength of the acid increases; this is illustrated in Table III which gives a list of acids, the first acid (acetic acid) giving the least deviation from the ideal curve, the others increasing in order to hydrochloric acid which gives the greatest deviation; this order is precisely the same as when the acids are arranged in order of increasing dissociation constants.

TABLE III

Acid	Dissociation Constant
Acetic	0.000018
β-hydroxy propionic	0.000031
α-hydroxy propionic	0.00014
Citric	0.00082
Tartaric	0.00097
Phosphoric	0.007
Hydrochloric	1.0

Systems consisting of water—base follow exactly the same rules as systems water—acid; the water may be here regarded as a weak base.

Double Compound Formation and Ionization

We may now consider the relation between double compound formation and ionization in solution.[10] Obviously there must be some connection between the two, since slightly ionized substances exhibit no appreciable hydrate formation, but as ionization increases combination becomes evident and where ionization is extensive marked compound formation occurs. The orthodox representation of the dissociation equilibrium, $RX \rightleftarrows R^+ + X^-$, relegates the solvent to the rôle of dead space and suggests no reason at all for any relation between hydration

[9] Acids containing the phenol group and amphoteric electrolytes are exceptions. See Kendall and Beaver, *J. Am. Chem. Soc.*, **43**, 1853 (1921).

[10] See Kendall and Booge, *J. Am. Chem. Soc.*, **39**, 2323 (1917).

and ionization. We may put the matter on a much more reasonable basis by adopting the view that ionization is preceded by combination between solvent and dissolved substance and is a consequence of such combination. Consider for example the system water—hydrochloric acid; in the liquid state when perfectly pure both are practically non-conductors of electricity; both contain unsaturated atoms in the simple molecules and are in consequence highly associated. Upon admixture we obtain a liquid possessing considerable conductivity and we regard this as being due solely to the dissociation of the hydrochloric acid into its constituent ions. There is, however, no reason at all why the conductance should be referred entirely to the hydrochloric acid and not at all to the water. It is possible to consider water as the ionizing substance in all conducting aqueous solutions, but a more reasonable viewpoint would give each component equal credit. It is known of course that the ions in this particular case are hydrated but the hydrated chloride ion $(Cl,H_2O)^-$ might just as well be called a solvated hydroxyl ion $(OH,HCl)^-$.

The hypothesis just advanced is that ionization in solution is preceded by the formation of solvent—solute complexes and disintegration of these into ions of opposite charge. The extent of ionization in any solution will consequently depend in the first place upon the extent of compound formation; that is, upon the degree to which reactions of the type $AB + CD \rightleftarrows AB,CD$ proceed from left to right in a mixture of AB and CD in the liquid state. In the second place the extent of ionization will depend upon the extent of the dissociation of these compounds into ions of opposite charge; that is, upon the degree to which reactions of the type $AB,CD \rightleftarrows A^+ + (B,CD)^-$ proceed from left to right in the same mixture. If the amount of compound formation is large and if these compounds are unstable ionically, the conductivity of the mixture will be high; if there is little combination or if the compounds formed are comparatively stable ionically, the conductivity of the mixture can be but small. We shall therefore be able to predict the extent of ionization in any solution when we have once established what factors affect the formation and the ionic stability of solvent—solute complexes. The first part of this problem has already been discussed and it has been shown that the stability of complexes with regard to their components increases with the differences in the positive or negative nature of the substituent groups of the components; this increase, however, makes the complex unstable ionically so that ionic dissociation is favored:

$$AB,CD \rightleftarrows A^+ + B,CD^-$$

A mixture of two saturated substances cannot give a conducting solution, and a solution of an unsaturated substance in a saturated liquid will also have a very low conductivity since double compound will be very slight. A mixture of two unsaturated substances, however, affords several possibilities and may be separated into three types.

The first type consists of mixtures in which the conductivity is not widely different from that of its components. This is typical of all mixtures in which the two components are similar in character, for there will only be slight compound formation and hence slight ionic dissociation; the conductivity will always be very small and will be much the same as its constituents in the pure state. Typical examples are furnished by a mixture of two very weak electrolytes such as water—methanol or two very strong electrolytes such as trichloroacetic acid—hydrobromic acid.

The second type consists of mixtures in which the conductivity is markedly greater than either of the pure components but is not exceptionally high. This is typical of mixtures in which the two components are somewhat divergent in character but not markedly so. Formation of complexes will be limited to the simplest type AB,CD and the degree of dissociation of this into its components AB and CD will be considerable. There will be a small production of the new ionic species A^+ and B,CD^-, so that the conductivity of the solution may considerably exceed that of its components without being especially high. Examples of this type are furnished by a mixture of any weak acid or weak base with water, or a mixture of hydrochloric acid with formic acid.

The third type consists of mixtures in which the conductivity is very great even if the mixture is formed from two practically non-conducting substances. If these are decidedly diverse in character extensive compound formation will occur on admixture and the complexes formed will include AB,CD and also larger ones $(AB)_x,(CD)_y$. Disintegration of these complexes into ions of opposite charge takes place very readily and renders the solution a good conductor. Examples of such solutions are given by any strong acid or strong base in water and also by a mixture of methanol and hydrochloric acid. The essential features of a solution of high specific conductivity are therefore, first, unsaturation in both components, and second, a decided difference in the character of the two components. The first is necessary to enable compound formation to occur at all, and the second is the driving force which regulates the increase in molecular complexity and hence in ionization of admixture. Table IV illustrates the working of the two factors unsatura-

tion and ionization. Many examples of this behavior are available; for example considering water as the dissolved substance Walden found that in liquid hydrocyanic acid it is a poor conductor, in formic acid it is a fair conductor while in sulfuric acid it is a good conductor.

TABLE IV

Unsaturation	Conductivity	Diversity
HCl—octane	Nonconductor	HCl—CCl_3COOH
HCl—benzene	Poor	HCl—$CH_2ClCOOH$
HCl—ether	Fair	
HCl—ethyl alcohol	Good	HCl—CH_3COOH
HCl—water	Excellent	

Electronic Theory and Complex Compounds

It is interesting to apply the ideas of the electronic theory of valence to these complex compounds.[11] On this theory the single bond between two elements is represented by a shared pair of electrons; in the non-polar bond so frequent in organic chemistry the electron pair is supposed to be midway between the two atoms whereas in the polar bond the electron pair is nearer one of the atoms. Liquid hydrochloric acid which is a non-conductor must consist mainly of the inactive covalent bonds whereas in aqueous solution the equilibrium must be almost completely shifted over to the active electrovalent type, $H^+ : Cl^-$. Negative elements or radicals on this theory are defined as those which draw towards themselves the electron pairs which constitute the outer shells of all neighboring atoms, whereas electropositive groups are those which repel or attract these electrons to a less extent. We may now consider the addition of an acid H : X to a ketone $\begin{matrix}R\\R'\end{matrix}> C : : \ddot{O} :$; the tendency of oxygen is to convert these lone electron pairs into bonds and naturally this tendency will be the greater when R and R′ are the more electropositive, because the double bond electrons are less strongly bound by the group $\begin{matrix}R\\R'\end{matrix}>C :$; similarly the more strongly negative the group X the more readily will the hydrogen leave it for the carbonyl group. This may be represented as follows:

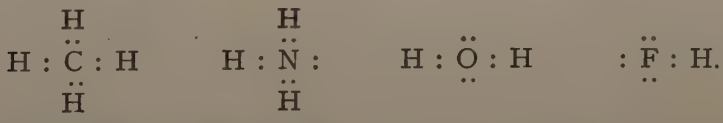
$$\begin{matrix}R\\R'\end{matrix}> C : : \ddot{O} : + H : X \rightleftarrows \left[\begin{matrix}R\\R'\end{matrix}> C : : \ddot{O} : H\right]^+ + X^-.$$

We shall, therefore, have extensive ionization when the electron affinity of X is large and the electron affinity of R and R′ is small. Thus we

[11] See Lewis, "Valence and the Structure of Atoms and Molecules," The Chemical Catalog Company, New York, 1923; also see a discussion of the Electron Theory of Valence in *Trans. Faraday Soc.*, 19, 450 (1923).

attach comparatively little importance to complex formation between the components.

In a recent paper Latimer and Rodebush [12] discuss polarity from this point of view; they point out that Abegg and Bodlander [13] were the first to give a comprehensive discussion of the general facts concerning strong and weak electrolytes, the solubility of salts and the formation of complex ions in solution. Abegg and Bodlander showed that these facts may be co-ordinated and explained to a surprising extent by attributing to each element or radical, in greater or less degree, a property which they called electro-affinity, but which has been more commonly designated electropositive or electronegative character. It now seems possible to go further and show this property to be a consequence of the structure of the atom. The ionizing property of a solvent has commonly been connected with the dielectric constant, the Nernst-Thomson rule stating that the ionizing power of a solvent should vary more or less directly with the dielectric constant. Since the powerful electrostatic forces between ions must be overcome before ionization can take place it seems reasonable to assume that the solvent can act as the depolarizing medium and partly neutralize these forces; the dielectric constant should give a measure of this power. Latimer and Rodebush conclude that when we consider the ionization of acids the dielectric constant becomes a secondary factor and that the ionization of acids, or indeed extreme polarity of any compounds involving hydrogen, must be interpreted as due to the transfer of a hydrogen nucleus from one molecule to another, thus forming a complex ion. Indeed the validity of the Nernst-Thomson rule has frequently been questioned. The conductivity of hydrochloric acid is not unduly high in such solvents as acetone, nitrobenzene or hydrocyanic acid although all have high dielectric constants. Walden [14] has shown that ionization of acids in solvents is independent of the Nernst-Thomson rule and is greater the more basic the solvent. Suppose we consider the following compounds:

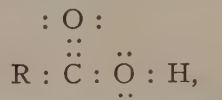


The increasing charge on the kernels of the elements from carbon to fluorine must tend to pull in closer the electrons of the octets formed

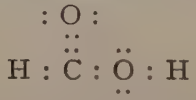
[12] Latimer and Rodebush, *J. Am. Chem. Soc.*, **42**, 1419 (1920).
[13] Abegg and Bodlander, *Z. anorg. Chem.*, **20**, 453 (1899).
[14] Walden, *Trans. Faraday Soc.*, **6**, 71 (1910).

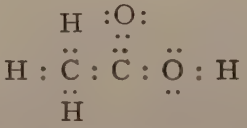
about the kernels; at the same time the hydrogen is held off by the increasing repulsion between the positive nuclei; consequently the total force holding the hydrogen becomes less, that is, the compound becomes more acid when dissolved in a solvent the molecules of which have a field sufficiently negative to pull the hydrogen away. We may now consider the tendency of these same hydrides to take up electrons. The methane molecule has the four pairs of electrons in its octet shared by two atoms and has therefore no free pairs of electrons left, while ammonia has one free pair of electrons, water two and hydrogen fluoride three. From these considerations we should expect ammonia to form readily the ion NH_4^+ and water and hydrogen fluoride to show strong but decreasing tendencies to form the ions, H_3O^+ and H_2F^+.

The ionization of organic acids may be explained[15] along similar lines. If we consider an acid of the type



we may conclude that whenever the nature of R is such as to exert a strong pull upon the electrons holding it to the carboxyl carbon, the acid will be correspondingly strengthened. It is interesting to compare formic acid and acetic acid;





the hydrogen kernel of formic acid exerts a much stronger pull on the electron pair between it and the carboxyl group than the methyl group of acetic acid; consequently the carbonyl hydrogen of formic acid is looser and will wander more readily.

Catalytic Activity and Double Compound Formation

We may now consider the relation between double compound formation, ionization and catalytic activity. From experience with water solutions we would infer that ionization and catalytic activity are approximately directly proportional. This simple proportionality fails when we consider other solvents and mixtures of solvents. Double compound formation and ionization occur to a much greater extent in the system water—hydrochloric acid than in the system ethyl alcohol—hydrochloric acid, but the catalytic activity of the two systems is in the ratio of about

[15] *See also* Lewis, *J. Am. Chem. Soc.*, **38**, 782 (1916).

1 : 1000 respectively. There does not seem to be any reason based on these theories why the ethyl alcohol system should be approximately one thousand times as active catalytically as the water system and yet this relation holds for many different reactions. The situation becomes still more mysterious when we consider that the addition of minute quantities of water (up to 0.2 per cent, for example) reduces the velocity in the ethyl alcohol system ten to one hundred times. The system ether—hydrochloric acid also gives quite unexpected results from the catalytic point of view, since the catalytic activity is apparently zero,[16] although compound formation and ionization should be present to a moderate extent. The addition of one to two percent of water causes the reaction to go with a very high velocity, far higher than in the system water—hydrochloric acid. It is evident that the relation between ionization and catalytic activity must be studied further since no hypothesis has been advanced to explain the observed facts in a satisfactory manner. It is probable that an explanation of these anomalies will be found by making a study of the catalytic activity of a number of systems consisting of acid—solvent, great care being taken to remove traces of impurities, especially water.

Carbonyl Chloride as Solvent

It has recently been pointed out[17] that our theory of solution has developed largely, if not entirely, from a study of systems which yield a hydrogen ion complex and a negative ion depending on the solvent used. From a purely theoretical standpoint, there is no more justification for the restriction of the idea "acid" to a hydrogen compound, as sulfuric or nitric acid, than there is for the restriction of the idea "base" to oxides or hydroxides of metals; the ammono bases, of which potassium amide KNH_2 is typical, are one well known group of bases not conforming to this idea. The actual discovery of a solvent, carbonyl chloride, commonly known as phosgene, which conforms to the general requirements of the parent substance of a system of acids, bases and salts, but which contains no hydrogen, makes it necessary to adjust our conception of an acid to include the new case, and to generalize our definitions relating to solvent systems.

We may consider the system carbonyl chloride—aluminum chloride. In the pure liquid state both substances have very small conductivities

[16] Taylor and Close, *J. Phys. Chem.*, **29**, 1095 (1925).

[17] Germann, *J. Am. Chem. Soc.*, **47**, 2461 (1925); see also Germann and Gagos, *J. Phys. Chem.*, **28**, 965 (1924); Germann and McIntyre, *ibid.*, **29**, 102 (1925); Baud, *Compt rend.*, **140**, 1688 (1905).

and are therefore very slightly ionized. When mixed, however, there is extensive compound formation and ionization. On electrolysis, carbon monoxide is liberated at the cathode and chlorine at the anode. The similarity to an aqueous solution of sulfuric acid is striking and we may therefore conclude that in the presence of a suitable substance carbonyl chloride will dissociate into the ions CO^{++} and Cl_2^{--}. A study of organic reactions with such substances would be of great interest.

Interpretation of Freezing Point Data

It is interesting to consider the reason for the successful interpretation of freezing-point data when used in connection with double compound formation as compared with other methods. Even such measurements as latent heat, vapor pressure or boiling-point, which are really all connected theoretically with the freezing-point method, have not been interpreted so successfully. It seems likely that the success of this method is due to the fact that its nature automatically compels the observer to make the measurement under the most favorable conditions for maximum double compound formation. Complex compounds are usually formed with evolution of heat and are more stable the lower the temperature; consequently measurements of a property of a liquid mixture should be made at as low a temperature as possible. It seems probable that part at least of the erratic and contradictory results obtained by the use of such measurements [18] as viscosity, heat capacity, light absorption or conductivity is due to making the measurements at temperatures when complex formation is slight. Viscosity measurements of binary systems at various temperatures [19] show that compound formation increases at lower temperatures and maxima appear at exactly equimolar concentrations.

Double Compound Formation with Aluminium Chloride

The most diverse types of carbon compounds have been found to unite with metallic chlorides, notably those of aluminium, iron, tin and antimony; and some authors present evidence that compounds even of benzene and other inactive hydrocarbons have been prepared.[20] Alumininum chloride exhibits a greater tendency to combine with the higher homologs of benzene than with benzene itself. For example in the

[18] A review of these is given by Washburn, *Tech. Quarterly*, **21**, 399 (1908); see also Turner, "Molecular Association," Longmans, Green and Co., London.

[19] Kurnakov and Schemtschushi, *J. Phys. Chem.*, **83**, 481 (1913).

[20] Gustavson, *J. pr. Chem.*, **68**, 209 (1903); *idem, ibid.*, **72**, 57 (1905); *idem, Compt. rend.*, **140**, 940 (1905); Schleicher and Buttgenbach, *J. pr. Chem.*, **105**, 355 (1923).

ethylation of benzene [21] the liquid separates into two layers, the lower layer consisting of aluminium chloride and the higher homologs of benzene, whereas the upper layer contains only a trace of aluminium chloride and most of the benzene and lower ethylated products. The evidence presented by Gustavson for the existence of the large number of double compounds that he enumerates is that the double compounds are liquids, insoluble in excess of the hydrocarbon and giving analysis approximately in single stoichiometric ratios.

It is evident, therefore, that a phase rule study of these systems would probably seriously diminish the number of double compounds formed. Such studies have been made by Menschutkin.[22] Investigation of the system benzene—aluminium chloride gave a freezing-point diagram of two curves meeting at the eutectic point; the crystalline phases of the two curves consist of benzene and aluminium bromide respectively, the diagram indicating that no compound is formed between the two constituents. Similar results were obtained with toluene and *p*-xylene. Aluminium bromide dissolves readily in ethylene bromide, but the freezing-point curve in this case also indicates that no isolable compound is formed.[23] On the other hand aluminium chloride and bromide readily yield a crystalline 1 : 1 compound with benzoyl chloride melting at 93° and 90° respectively. Benzophenone yields similar 1 : 1 compounds, the compound with the chloride melting at 130° and the compound with the bromide melting at 142°. Acetophenone yields similar compounds but the system is difficult to investigate, since the salts crystallize with great difficulty and readily yield resinous products.[24]

The study of the nitro derivatives of benzene gave very interesting results.[25] Combination between aluminium chloride and nitrobenzene is very extensive as is shown by the isolation of two compounds, $AlCl_3$, $C_6H_5NO_2$ and $AlCl_3,2C_6H_5NO_2$. The *o*- and *m*-nitrotoluenes also give two compounds of similar constitution but the *p*-nitrotoluene gives only a 1 : 1 compound. The three chloronitrobenzenes and the three bromonitrobenzenes all form 1 : 1 compounds with aluminium chloride. Aluminium bromide gives exactly similar compounds in all cases except that it forms no 1 : 2 compounds. The compounds with aluminium chloride practically always melt at higher temperatures than the corresponding compounds formed by the bromide.

[21] Milligan and Reid, *J. Am. Chem. Soc.*, **44**, 206 (1922).
[22] Menschutkin, *J. Russ. Phys. Chem. Soc.*, **41**, 1053, 1089 (1909).
[23] *Idem, ibid.*, **42**, 1308 (1910).
[24] *Idem, ibid.*, **42**, 1298 (1910).
[25] *Idem, ibid.*, **41**, 1053 (1909); *idem, ibid.*, **42**, 58 (1910).

Boeseken [26] has prepared a number of compounds between aluminium chlorides and acid chlorides. The method usually followed was to dissolve molecular proportions of the two substances in some solvent, evaporate off the excess of solvent and analyze the crystalline residue. Without a freezing-point diagram it is not possible to obtain very much insight into the stability of these compounds, but it is evident from the behavior of the compounds that aluminium chloride can combine fairly strongly with one molecule of many acid chlorides.

Compounds of aluminium chloride with acetyl chloride and its homologs, chloroacetyl chloride, *p*-bromobenzenesulfonyl chloride, and many others, have been prepared by Boeseken in the course of his researches into the mechanism of the Friedel and Crafts reaction.

Aluminium chloride and ether form a 1 : 1 compound [27] which crystallizes in large plates from carbon disulfide; a solution of aluminium chloride in ether is only very feebly conducting. Walker and Spencer prepared 1 : 1 compounds between aluminium chloride and ethyl benzoate, ethyl oxalate, ethyl malonate, anisol, *o*-nitrotoluene and *m*-dinitrobenzene. Methyl mandelate and acetic acid give compounds containing four molecules of aluminium chloride to one molecule of the organic compound.

Henderson and Gangloff [28] noted that aluminium chloride removed unsaturated hydrocarbons from gasoline and investigated the action of aluminium chloride upon a number of unsaturated compounds. In the dry state combination with acetylene or ethylenic hydrocarbons is slow and tars are usually produced; in solution, however, addition compounds are formed containing usually one or more molecules of the solvent in combination. Ashan [29] has noted that there is no action between ethylene and aluminium chloride dissolved in carbon disulfide.

Double Compounds with Other Metallic Halides

Magnesium bromide and magnesium iodide combine extensively with a great variety of organic substances; [30] they both dissolve in ether

[26] Boeseken, *Rec. trav. chim.*, (a) **19**, 19 (1900); (b) **20**, 102 (1901); (c) **22**, 301 (1903); (d) **23**, 98 (1904); (e) **24**, 6 (1905); (f) **30**, 148, 381 (1911); (g) **31**, 367 (1912); (h) **32**, 1 (1913).

[27] Walker and Spencer, *J. Chem. Soc.*, **85**, 1106 (1904); Plotnikov, *Z. anorg. Chem.*, **56**, 53 (1907); Frankforter and Daniels, *J. Am. Chem. Soc.*, **37**, 2560 (1915).

[28] Henderson and Gangloff, *J. Am. Chem. Soc.*, **38**, 1382 (1916); Gangloff and Henderson, *ibid.*, **39**, 1420 (1917).

[29] Ashan, *Ann.*, **324**, 1 (1902).

[30] Menschutkin, *J. Russ. Chem. Soc.*, **35**, 610 (1903); *idem, Bull. St. Petersburg Polytechnic Inst.*, vols. 3, 4 (1905); *idem, Z. anorg. Chem.*, **49**, 207 (1906); Zelinsky, *J. Russ. Phys. Chem. Soc.*, **35**, 399 (1903); Menschutkin, *ibid.*, **39**, 102

and form an isolable 1 : 1 compound and a 1 : 2 compound with ether respectively. When the di-etherates are dissolved in an alcohol, organic acid, acid anhydride, ester, aldehyde, ketone or acetal, the ether is displaced by the solvent and a compound between the magnesium salt and the solvent (usually 1 : 6) may be crystallized out. The solubility curves of the 1 : 6 complex compounds very much resemble the solubility curve for $MgX_2,6H_2O$ in water. The compounds with methylal have the formula $MgX_2,2CH_2(OCH_3)_2$, and magnesium bromide gives a 1 : 1 compound with both acetyl chloride and benzoyl chloride. The magnesium halides show ready and extensive addition compound formation with many organic compounds containing nitrogen, such as aniline, acetamide, urethane, carbamide, acetanilide and acetonitrile; all of these substances form complexes consisting of one molecule of halide with six molecules of the organic compound and in most cases other complexes containing a lower proportion of organic compound exist. Menschutkin also studied certain molecular compounds of calcium chloride [31] which apparently does not display quite as great a tendency towards complex compound formation as the bromide or iodide of magnesium; the compounds with alcohols have the general formula $CaCl_2$, 3ROH; with acids $CaCl_2$, 4RCOOH; and with esters $CaCl_2$, 2RCOOR'. With acetals, calcium chloride forms isolable 1:1 compounds.

The addition compounds of antimony trichloride and antimony tribromide with a great variety of organic substances have been carefully studied.[32] These halides show a very strong tendency to combine with organic compounds as shown by the great number of complex compounds isolated. It is of particular interest to note that while none of the magnesium or aluminium halides form an isolable compound with benzene, the two additive compounds $C_6H_6,2SbCl_3$ and $C_6H_6,2SbBr_3$ have been isolated. On the other hand neither cyclohexane or cyclohexene yield isolable compounds with the antimony halides.

The occurrence of extensive complex compound formation between organic substances [33] and metallic salts, many of which are used as catalysts, seems particularly significant from the point of view of reaction mechanism and will be discussed further in connection with the particular reactions.

(1907); *idem, Z. anorg. Chem.*, **54**, 89 (1907); *idem, J. Russ. Phys. Chem. Soc.*, **38**, 3 (1906).

[31] Menschutkin, *J. Russ. Chem. Soc.*, **38**, 1010 (1906).

[32] See Menschutkin, *J. Russ. Phys. Chem. Soc.*, 1910-1914.

[33] For a more extended treatment of organic addition compounds see Pfeiffer, "Organische Molekularverbindungen," Zweite Auflage. Enke.

Chapter IV.

Theoretical.

The theoretical problems arising from the study of slow reactions are manifold, and the difficulties are not diminished by the number of answers that have been proposed. The first theoretical difficulty lies in the very existence of these slow reactions. If we add ethyl alcohol to acetic acid, an intimacy of mixture occurs far greater than we could ever achieve by grinding together two solid substances; after the first few minutes of mixing each molecule of ethyl alcohol must have collided millions of times with acetic acid molecules, yet after weeks of standing in this intimate contact we find that only a negligible proportion of the molecules have combined to form ethyl acetate. If we add to the mixture certain substances which contain hydrogen ion or hydroxyl ion we find that the rate of the reaction is greatly speeded up so that it may reach equilibrium in the course of a few minutes. Furthermore, if we measure the rate at which the reaction proceeds at 25° and 35°, for example, we find that the rate at the higher temperature is about two and a half times as great as the rate at the lower temperature. These three experimental results have so far remained almost a complete mystery; their importance lies in the fact that they are common to the great bulk of organic chemical reactions and their fascination is shown by the great number of papers on this subject published in recent years.

Perhaps the first question which might occur to one is whether there is any "natural" rate of the reaction between acetic acid and ethyl alcohol; that is, if we purified the reactants rigorously from all traces of catalytic impurities, would there be a measurable rate of combination or would the two substances remain together indefinitely without combining? It is not possible to answer this question for acetic acid and ethyl alcohol because the natural rate, if it exists, is too slow to be measurable. If, however, a reaction could be found which is catalytic and which after careful removal of all traces of catalytic influence still had a measurably fast rate, it would be reasonable to assume that this is the natural rate of the reaction. However, such a reaction has not yet been found.

From the theoretical point of view it seems reasonable enough to postulate the existence of a natural rate. The distribution of energy between the ethyl alcohol molecules and between the acetic acid molecules as described by the Maxwell-Boltzmann law means that some of the molecules are in a highly energized state. Doubtless the collision of ethyl alcohol and acetic acid in certain of these activated states leads to the formation of ethyl acetate independently of any catalyst. We may also speculate as to whether the catalytic reaction is a separate and independent reaction from the natural reaction or whether the catalyst simply hastens the natural reaction. Even at the very beginning our hypotheses must diverge considerably and we have no experimental test as to which is the right direction.

Another fundamental point which we must consider at the outset is our method [1] of representing the reaction between two substances *A* and *B*. The usual method of representing the rate at which this reaction takes place, as proportional to the concentrations of *A* and *B*, rests simply on the probability of collision between the *A* and *B* molecules. If, however, the rate is dependent only on the probability of collision one might expect the velocity to be independent of the specific nature of the reaction, being simply determined by the temperature, the mean free path and the speed of the molecules. However, owing to the highly specific nature of reaction velocity as well as to the remarkable effect brought about by a change in temperature, it has usually been necessary to bring in other factors besides the mere probability of collision. Also, on this basis, all our reactions in which the reacting substances are at any kind of measurable concentration, should occur practically instantaneously.

In connection with probability of collision there arises at once a factor [2] which may be illustrated by the rate of reaction between ketones and iodine. Since one of the α-hydrogens of a ketone is substituted by iodine, presumably the collision between the ketone and iodine must occur in the neighborhood of the carbonyl group. We might suspect on this basis that acetone and iodine would react faster than dipropyl ketone and iodine, because in the latter case there must be many ineffective collisions. However, this factor does not seem to be of great importance. Actual measurements [3] show that some of the

[1] This is discussed by W. C. McC. Lewis, *Brit. Assoc. Adv. Sci. Rep.*, 394 (1915).

[2] See Stern, *Ann. Physik.*, **44**, 497 (1914); Dushman, *J. Am. Chem. Soc.*, **43**, 397 (1921); Bjerrum, *Z. physik. Chem.*, **108**, 87 (1924).

[3] Rice and Fryling, *J. Am. Chem. Soc.*, **47**, 379 (1925).

higher saturated aliphatic ketones react faster than acetone. Furthermore, studies of the rates of hydrolysis of different esters of the same acid show that the size of the alcohol radical does not have any very marked effect on the velocity.

The difficulties in formulating a theory of reaction rates based on collisions has led to a view which postulates in its extreme form that what we are measuring is a rate of reaction between one of the reactants and infra-red radiation. This view seems sufficiently reasonable when we consider the large number of photochemical reactions in which it is necessary for one of the reactants to become activated by absorbing light of a characteristic frequency. This idea is attractive because the density of radiation of frequency ν is proportional to $e^{-h\nu/kT}$ and hence the relation between reaction rate and temperature on this basis should be that given by the Arrhenius equation. The development of this point of view has mainly been the work of Perrin [4] and W. C. McC. Lewis.[5] In a discussion of the mechanism of chemical reactions, Tolman [6] states: "Although there are a number of considerations which show, as we shall see, that the radiation theory in its simple form cannot give a valid account of the mechanism of all reactions, nevertheless we cannot but admire the boldness and beauty of this conception which would unify our pictures of thermal and photochemical reactions and account in the simplest possible manner for the orders of reaction by providing a method of activation which is independent of concentration." This point of view does not of course exclude activation by other means. We know that energy can be transferred from electrons to atoms and molecules by collision and in certain cases by atoms and molecules; for example,[7] an excited mercury atom can by collision dissociate or activate a hydrogen molecule. It is, therefore, quite possible that our ordinary thermal reactions may be such that the energy transfer takes place by collisions of the reactants and not through transfer of infra-red radiation. Usually discussions of reactions on this basis assume a mechanism of activation so fast, compared to the rate of reaction, as to maintain the full Maxwell-Boltzmann quota of molecules in the activated state. Since this quota is proportional to $e^{-E/RT}$, where E is the energy of activation, it is easy to see again why the relation between reaction rate and temperature should be that given by the Arrhenius equation.

[4] Perrin, *Ann. Phys.*, **11**, 5 (1919).
[5] Lewis, *J. Chem. Soc.*, **113**, 471 (1918); *idem*, *Phil. Mag.*, **39**, 26 (1920). A review of the subject is given by Harned, *J. Franklin Inst.*, **196**, 181 (1923).
[6] Tolman, *J. Am. Chem. Soc.*, **47**, 1524 (1925).
[7] Cario and Franck, *Z. physik. Chem.*, **11**, 161 (1922).

The two effects, namely radiation and molecular collisions, are inextricably mixed in chemical reactions as ordinarily conducted. It does not seem possible that we shall be able to solve the riddle until some method is devised whereby we can diminish or remove one of the effects and compare the rate of the reaction with the rate under normal conditions. In this connection the study of gaseous reactions offers special advantages, because by diminishing the pressure the effect of molecular collisions can be greatly diminished, whereas the density of radiation is unchanged. In two recent papers [8] several reactions have been studied at very low pressure, and definite abnormalities have been found to occur. Hinshelwood's paper is of especial interest to organic chemists since he has shown that the homogeneous gaseous decomposition of propionic aldehyde, of diethyl ether and of dimethyl ether are unimolecular at high pressures but bimolecular at lower pressures; the explanation of these quasi-unimolecular reactions is quite uncertain.

There is however a much more powerful method of investigating chemical reactions, in which molecular collisions are practically completely excluded. Suppose we have a glass tube containing three diaphragms each of which has a small hole through the center; the three small holes are arranged in a straight line along the axes of the tube. The lower end of the tube contains a little nitrogen pentoxide and is kept at —100°; the upper portion around the diaphragms and above is kept at liquid air temperature. The whole tube is evacuated to about 10^{-6} mm. Nitrogen pentoxide has a very small vapor pressure at —100° but the vapor pressure is negligibly small at liquid air temperatures; consequently we shall have coming from the third hole a beam of nitrogen pentoxide molecules in which practically no collisions of the molecules take place, either between themselves or between the molecules and the walls of the vessel.[9] The molecules in the beam have the Maxwellean distribution of velocities so that the only collisions that can occur are when fast moving molecules overtake slow moving molecules. The number of such collisions is negligibly small.

A great number of interesting experiments may be performed with such a beam. We may, for example, surround the beam by a cylindrical furnace heated to 200°. We know the velocity of the molecules and consequently the time they remain in the furnace; we can analyze microchemically the nitrogen pentoxide that passes through the furnace

[8] Hirst and Rideal, *Proc. Roy. Soc.*, **109A**, 526 (1925); Hinshelwood, *ibid.*, **114**, 84 (1927).

[9] For a more detailed explanation of methods of obtaining molecular beams, see Stern, *Z. physik. Chem.*, **39**, 751 (1926).

and compare the rate of decomposition with the rate under ordinary conditions. In the event of infra-red radiation failing to decompose the molecules it is possible to subject the beam to ultra-violet light where the quanta are very much larger. Another experiment may be devised in which the beam is allowed to impinge on a heated surface; when the molecules bounce off the surface they immediately condense on the walls of the tube and may be collected and analyzed.[10]

Work of a similar nature has recently been published [11] in which a beam of iodine molecules pass through a platinum cylinder heated to 1100°; within the limits of experimental error there was no decomposition into atoms. Arrangements were also made in which streams of two different vapors were allowed to impinge on one another and the products examined. It seems probable that such experiments will enable a decisive test to be made of the merits of the rival hypotheses as to the mechanism of chemical action.

The fact that so many chemical reactions proceed slowly has always been a great theoretical difficulty and in most of the papers dealing with the theoretical side of the subject it is usually pointed out that all the molecules cannot be in the same state, otherwise the reaction rate would be zero or infinite. We may for more definiteness consider the hydrolysis of methyl acetate:

$$CH_3COOCH_3 + H_2O = CH_3COOH + CH_3OH.$$

On this basis the methyl acetate molecules are not all alike chemically; the great bulk of the molecules are inert and do not react on collision with a water molecule; there are however an "activated few" that have acquired a much greater energy than the average and on collision with a water molecule these react. These active molecules are considered to be only a very minute fraction of the whole and they may have acquired their extra energy either through fortunate collisions or through momentary possession of an excess of infra-red energy. We have now to consider two reaction rates, namely, the rate at which the active methyl acetate molecules acquire their critical increment of energy and secondly the rate at which the active molecules react with water to give acetic acid and methanol; usually it is assumed that the rate of activa-

[10] This work, under the direction of the author and Dr. H. C. Urey, is now in progress in this Laboratory. Mr. R. N. Washburne has shown that it is possible in one hour to obtain sufficient nitrogen pentoxide for analysis. Mr. L. A. Staib has shown that when nitrogen pentoxide impinges on a heated surface under conditions such that the nitrogen pentoxide molecules do not collide with each other, the amount of decomposition is negligibly small.

[11] Kroger, *Z. physik. Chem.*, 117, 387 (1925).

tion is very fast compared to the rate of hydrolysis. Such hypotheses as these therefore postulate a "natural rate" for chemical reactions; the action of a catalyst is supposed in some way (depending on the particular hypothesis) to increase the fraction of the active molecules and hence increase the velocity of the reaction.

Now we have, of course, no evidence at all that methyl acetate exists in two forms which are chemically different; *a priori,* it is just as reasonable to say that the hydrogen-ion catalyst exists in two forms and that the reaction we are measuring is the rate of collision between methyl acetate and active hydrogen ions. On this basis any natural reaction between methyl acetate and water is completely neglected.

The remainder of this chapter is devoted to a discussion in greater detail of the various hypotheses advanced to explain the difficulties in connection with reaction rates. They are given in chronological order because it is not possible at present to decide if any of the points of view is correct.

Arrhenius Hypothesis

The Arrhenius hypothesis was advanced mainly with the intention of explaining the abnormally high temperature coefficients of chemical reactions. In a solution of cane sugar, for example, Arrhenius assumes that there are two kinds of molecules, one sort of which can be attacked or inverted by the acid, the other cannot. He regards the two types as different chemical species in tautomeric equilibrium; the amount of the active kind is extremely small as compared with the amount of the passive kind. If we let c be the total concentration of cane sugar and a be the concentration of the active form we have,

$$\frac{(c-a)}{a} = K$$

where K is the equilibrium constant of the reaction. Considering the reaction at two temperatures 25° and 35°, we obtain

$$a_{35}/a_{25} = K_{35}/K_{25}$$

since the term $(c-a)$ can be regarded as approximately equal to c. Arrhenius assumed that the rate of reaction depended upon the concentration of active molecules and upon nothing else so that we have

$$K_{35}/K_{25} = a_{35}/a_{25} = k_{35}/k_{25},$$

where k_{35} and k_{25} are the specific reaction rates at the two temperatures. The integrated form of the van't Hoff isochore gives us a relation

between K_{35} and K_{25} and the heat of the reaction, active molecules ⟶ passive molecules.

$$ln \frac{K_{35}}{K_{25}} = \frac{Q}{R}\left(\frac{1}{298} - \frac{1}{308}\right)$$

If the active molecules have 20,000 calories per mole more than the passive molecules ($Q = 20{,}000$ cal.) we can readily calculate that $K_{35}/K_{25} = 3.1$ (approximately); hence the temperature coefficient of the reaction k_{35}/k_{25} has also the value 3.1. For cane sugar hydrolyzed by hydrochloric acid k_{35}/k_{25} is approximately 4, so that we can calculate that the heat of the reaction, active cane sugar ⟶ passive cane sugar is 26,000 calories per mole. Other temperature coefficients would correspond to other heats of transformation from inactive to active molecules.

The Arrhenius equation is only empirical unless the somewhat unlikely discovery is made that all the substances which take part in slow reactions exist in two tautomeric forms in equilibrium. This is easily seen from van't Hoff's treatment;[12] if a reaction and the reverse reaction have independent specific reaction rates, the ratio between these constants must be the equilibrium constant which varies with the temperature according to the equation

$$\frac{d\, ln\, K}{dT} = \frac{Q}{RT^2},$$

where Q is the heat of the reaction. Writing K as the ratio of the two specific reaction rates, k_1 and k_2, this equation may therefore be broken into two equations,

$$\frac{d\, ln\, k_1}{dT} = \frac{A_1}{RT^2} + B$$

$$\frac{d\, ln\, k_2}{dT} = \frac{A_2}{RT^2} + B$$

At every temperature B is the same for both reactions and A_1 and A_2 are quantities such that their difference is the heat of the reaction; as pointed out by Lewis and Smith[13] this is all that can be learned about reaction velocities from thermodynamics alone.

Arrhenius extended his hypothesis to explain catalysis by assuming that the hydrogen-ion or other catalyst shifts the equilibrium between active and passive molecules to the active side and therefore increases the velocity of the reaction.

[12] Van't Hoff, "Studies in Chemical Dynamics," The Chemical Publishing Co., Easton, Pa., 1896.

[13] G. N. Lewis and Smith, *J. Am. Chem. Soc.*, 47, 1508 (1925).

It is apparent that several objections to this hypothesis arise at once, the chief being the somewhat artificial assumption of the existence of two tautomeric forms of substances, one being active and the other not. There is no reasonable evidence for assuming that two such forms exist. Such a postulate would lead to the conclusion that each reaction has a unique temperature coefficient depending upon the heat of activation of the substance or substances undergoing change. Furthermore, there does not seem to be any reason for picking out one reactant rather than another when postulating active and inactive molecules. For example, in the acid hydrolysis of cane sugar there are three substances taking part in the reaction, cane sugar, water and hydrogen ions; any one or all of the three might be present in two forms but we have no *a priori* ground for making a selection.

Finally, there is the arbitrary assumption, made to account for catalysis, of the shift of the equilibrium between active and inactive molecules. One of the characteristics of a catalyst is that it does not affect equilibrium states.

The Arrhenius hypothesis has not been developed to a stage where it can be put to a decisive test, and it can hardly be regarded as more than artificial until evidence is forthcoming of the existence of active and inactive tautomeric forms of substances.

Radiation Hypothesis

The fundamental assumption of the radiation hypothesis is based on analogy with photochemical reactions. Ordinary thermal reactions are assumed to be conditioned by the reaction between matter and infra-red radiation present throughout all matter. Trautz,[14] who first suggested that ordinary thermal reactions are dependent upon infra-red light, took as his fundamental assumption that a molecule must absorb a certain amount of energy in the form of infra-red light to become active; if Q is the heat of activation and α is the fraction of the total molecules in the active state at temperature T, he deduced the equation

$$\frac{\mathrm{d}\, ln\, \alpha}{\mathrm{d}T} = \frac{Q}{RT^2}.$$

Since the specific rate of a reaction is proportional to the fraction α of the molecules in the active state, the equation becomes similar in form to the Arrhenius empirical equation. From measurements of temperature

[14] Trautz, *Z. Wiss. Photochem.*, **4**, 160 (1906); *idem*, *Z. anorg. Chem.*, **102**, 81 (1918); for a more recent discussion of Trautz' views, see Essex and Gelormini, *J. Am. Chem. Soc.*, **48**, 882 (1926).

coefficients Trautz calculated the value of α for certain bimolecular reactions, and showed that there was good agreement between the measured rate of the reaction and the rate calculated on the assumption that the active molecules reacted at a rate determined by ordinary kinetic considerations.

It may be noted that a great many attempts have been made to develop a satisfactory theoretical interpretation of the empirical Arrhenius formula,[15] which may be written in the form,

$$k = S\, e^{-Q/RT}$$

where k is the specific reaction rate, S is a quantity which has the dimensions of frequency and is experimentally found to be nearly constant, Q is a constant which has the dimensions of energy and is also experimentally found to be nearly constant, and R and T have their customary significance. The more common interpretation of this equation may be expressed roughly in words as follows: the rate of a bimolecular reaction is given by the total number of collisions per minute between the two reactants multiplied by a fraction, $e^{-Q/RT}$, which represents the portion of the collisions occurring between molecules which have in some way or other attained an activated state so that a chemical change follows the collision.

Arrhenius based his considerations on the assumption that reacting substances exist in two tautomeric forms and that only the "active" form can react. He therefore takes Q as the heat of the reaction when the "passive" forms of the reacting substances change into the "active" forms. Marcelin,[16] on the basis of certain statistical mechanical considerations, finds Q to be the energy of the molecules in the "active" state minus their mean energy. Lewis and Perrin take Q as the radiant energy, $Nh\nu$ of activating frequency ν, which must be absorbed in order to put the molecules into a reactive condition.

Perrin was led to the radiation theory by a consideration of unimolecular reactions such as the dissociation of phosphonium chloride,

$$PH_4Cl \longrightarrow PH_3 + HCl.$$

Assuming the validity of the mass action law it is evident at once that the mass of gas transformed per minute is independent of the volume occupied and so the average life of a molecule before transformation is, at a given temperature, independent of the frequency of collisions. We may venture to go to the limit and consider a molecule in a vacuum at

[15] See Tolman, *J. Am. Chem. Soc.*, 43, 269 (1921).
[16] Marcelin, *Ann. Phys.*, 3, 120 (1915); *idem, Comp. rend.*, 158, 161 (1914).

constant temperature. This isolated molecule is broken up and transformed suddenly, without having undergone any collision, after an average life as long as that which it would have if the enclosure were full of gas and the molecule suffered in the same period millions of collisions. Perrin concludes that "the agent which can break up and re-make the molecule in a vacuum and make it conform to temperature is the same which imposes a definite temperature upon a thermometer suspended in a vacuum. It is, in the most general sense of the word, radiation, isothermal under stationary conditions, which fills the enclosure at each instant and in which the molecule remains immersed."

The most significant and fundamental assumption was made by W. C. McC. Lewis,[17] that the frequency, ν of the radiant energy which is capable of promoting a reaction may be calculated from the heat of activation Q by the formula $Q = Nh\nu$. For example, the heat of activation of cane sugar can be calculated from the temperature coefficient of the reaction to be 1.6×10^{-12} ergs per molecule; assuming that a cane sugar molecule becomes activated by one quantum ($N = 1$) we may calculate ν to be 1.23 μ, which is in the short infra-red, in a region in which sucrose shows strong absorption. This appeared to be a good vindication [18] of the original hypothesis, since the calculated wave length might have had any value. Further work, however, showed [19] that the radiation hypothesis was far from satisfactory. The vast majority of slow chemical reactions are certainly not unimolecular, so that Perrin's conclusions lack pertinence. When a chemical reaction such as the hydrolysis of cane sugar is placed in direct sunlight the rate is not appreciably affected, although the density of the absorbable infra-red radiation is increased about 10^{13} times.

Recently several papers [20] have appeared making a critical examination and summing up of the radiation hypothesis. Christiansen and Kramers conclude, from their analysis of a number of reactions classed as unimolecular, that the rate of activation cannot be accounted for, either on a basis of activation by collisions or activation by radiation. This difficulty which was first raised by Langmuir [21] seems sufficiently great so that the special radiation theory, which assumes activation by nearly

[17] Lewis and co-workers, *J. Chem. Soc.*, 1914-1922.
[18] See also H. A. Taylor and Lewis, *J. Chem. Soc.*, **121**, 665 (1922); Daniels, *J. Am. Chem. Soc.*, **48**, 607 (1926).
[19] See *Trans. Far. Soc.*, **17**, 546 (1922), for a discussion of the radiation hypothesis.
[20] Christiansen and Kramers, *Z. physik. Chem.*, **104**, 451 (1923); Lewis and Smith, *J. Am. Chem. Soc.*, **47**, 1508 (1925); Tolman, *ibid.*, **47**, 1524, 2652 (1925).
[21] Langmuir, *J. Am. Chem. Soc.*, **42**, 2190 (1920).

monochromatic light must be modified, because, for example, the rate of activation of nitrogen pentoxide molecules on this basis is far below the rate of decomposition of the gas. Christiansen and Kramers meet this difficulty by postulating that the molecules resulting from a chemical change will first be formed in an activated condition and only later fall to their normal state. They are therefore forced to conclude that the greater part of the activation results from the heat set free by the reaction itself. In other words they postulate a reaction chain: "We imagine the exothermic reaction $n \rightarrow n' + n''$, and consider that after activation through collision (or through radiation) an elementary reaction has taken place. Then we know that the products of the reaction immediately after the decomposition, must contain the energy of activation as well as the reaction energy measured by direct calorimetry (at least if no radiation is emitted in the spontaneous decomposition, as we must assume on account of the large constant of the decomposition rate.) Then evidently the reaction products rich in energy can activate new molecules through collision, which means the occurrence of so-called reaction-chains." Lewis and Smith point out two objections to this hypothesis, first, that the reactions which Christiansen and Kramers consider are not exothermic but endothermic, and second, that the decomposition of nitrogen pentoxide occurs at approximately the same rate in the gaseous phase and when dissolved in carbon tetrachloride or chloroform. To meet the second objection it would be necessary to make the very improbable assumption that the solvent molecules are quite incapable of taking energy from the "hot" molecules resulting from the decomposition. By assuming that the total internal energy of a molecule may be included in the energy of activation Lewis and Smith conclude that radiation can provide more than enough opportunities for activation.

Since it is practically universally assumed that at least some of the reacting molecules in slow chemical changes are in specially activated states it seems desirable to discuss the actual mechanism of the processes by which the quota of activated molecules is maintained. Tolman (*loc. cit.*) discusses the following mechanisms which have been proposed at one time or another:

a. Activation by collision with another molecule of sufficiently high kinetic energy (ordinary collision).

b. Activation by collision with another molecule which is itself in an activated state, resulting in a transfer of energy of activation (collision of the second kind).

c. Activation by the absorption of monochromatic radiation of the

frequency calculated from the temperature coefficient of the reaction rate (simple radiation theory of chemical reaction).

d. Activation by interaction with more than one frequency (elaborated radition theory of chemical reaction).

Tolman discusses very fully the possibility of activation by these four mechanisms and part of his conclusion which may also be used to sum up the present position of the radiation hypothesis is: "In conclusion it can be stated that activation may occur to some extent by all the four mechanisms suggested. Indeed since the great difficulty is to account for the rapidity with which energy of activation is supplied, we must not despise the assistance afforded by any method of activation. However, it seems at the present as if our main hopes must be centered on the elaborated radiation theory if we are to account for unimolecular reactions, and on this theory in general if we desire to have the same mechanism of activation for all typical chemical reactions." The most promising form of the elaborated radiation theory referred to is the absorption of a continuous range of frequencies. Actual reactions known in photochemistry often are produced by the absorption of such a continuous range of frequencies. In terms of the quantum theory this is to be interpreted as meaning that instead of a single activated state we have a whole range of activated states of continuously increasing energy content. Tolman concludes that this is the most hopeful modification of the radiation theory, for the great increase in the number of activated states would greatly increase the rate of activation.

Skrabal's Hypothesis

Skrabal [22] has written a comprehensive paper on the relation between reaction velocity and temperatures. He first refers to the ratio k_{T+10}/k_T and to the rule that for any reaction the value of this ratio diminishes as the temperature rises; reaction velocity, however, is influenced not only by the temperature but also by the catalysts, the nature of the medium, the order of the reaction, the chemical nature of the reactants, the concentration of the reactants and the presence of neutral salts; all of these factors including the temperature effect are referred to as "parameters of the reaction velocity." He then postulates (on grounds of analogy) that the effect of all the parameters is the same as the temperature parameter, namely, that with increasing value of the parameter, the ratio k_{T+10}/k_T diminishes. Much of the paper is devoted to the illustration and exposition of this parameter rule.

[22] Skrabal, *Monatsh.*, 37, 495 (1916).

He also postulates that reactions are ordinarily preceded by complex compound formation of the reactants, and that the following relation holds:

$$k'/k = K^n,$$

where k is the velocity of the first reaction, K is its equilibrium constant, k' is the velocity of the second reaction and n is the order of the reaction as used in the velocity equation.

In a series of papers published during the past fifteen years Skrabal has studied the very complicated reactions of halogens in alkaline buffer solutions. He finds that the order of these reactions varies from 3 to 14 and the temperature coefficients from 0.8 to 100. The results obtained are in accord with the foregoing rules, but it seems unlikely that these rules can apply to reactions in general.

Activity Hypothesis

Many attempts have been made to replace the concentration terms in the velocity equation by other factors which would give a satisfactory constant for k under varying conditions.[23] Van't Hoff suggested that the active mass of a substance was determined by its solubility as well as by its concentration. Arrhenius about the same time suggested that osmotic pressures and not the actual concentrations should be considered in deducing reaction velocities. Arrhenius notes that the velocity of inversion of cane sugar is much more nearly proportional to the osmotic pressure than to the concentration, and that foreign substances in general increase the osmotic pressure of a compound, so that they should also in general accelerate the velocities of reaction, which is actually the case. His later work with Anderson [23] gives further support to these views. Buchböck [23] attempted to test the views of van't Hoff by measuring the rate of hydrolysis of carbonyl sulfide in a large number of different

[23] Bibliography: Van't Hoff, "Lectures on Theoretical and Physical Chemistry," Eng. ed., **1898**, Part 1, p. 217; Arrhenius, *Z. physik. Chem.*, **28**, 317 (1899); Buchböck. *Z. physik. Chem.*, **34**, 229 (1900); Loomis and Acree, *Am. Chem. J.*, **46**, 632 (1911); Harned, *J. Am. Chem. Soc.*, **37**, 2460 (1915); *idem, ibid.*, **40**, 1461 (1918); Harned and Selz, *ibid.*, **44**, 1475, 2968 (1922); Harned and Pfanstiel, *ibid.*, **44**, 2193, 2969 (1922); Åkerlöf, *Z. physik. Chem.*, **98**, 260 (1921); Arrhenius and Anderson, *Medd. K. Vetenskapsakad. Nobelinst.*, **3**, No. 25, 1 (1918); Jones and Lewis, *J. Chem. Soc.*, **117**, 1120 (1920); Scatchard, *J. Am. Chem. Soc.*, **43**, 2387 (1921); Moran and Lewis, *J. Chem. Soc.*, **121**, 1613 (1922); Scatchard, *J. Am. Chem. Soc.*, **45**, 1580 (1923); Garrett and Lewis, *ibid.*, **45**, 1091 (1923); Brönsted, *Z. physik. Chem.*, **102**, 169 (1922); Brönsted and Pedersen, *ibid.*, **108**, 185 (1924); Brönsted and Teeter, *J. Phys. Chem.*, **28**, 579 (1924); Brönsted and King, *J. Am. Chem. Soc.*, **47**, 2523 (1925); Kilpatrick, *ibid.*, **48**, 2091 (1925); Bjerrum, *Z. physik. Chem.*, **108**, 82 (1924); Brönsted, *ibid.*, **115**, 337 (1925); Åkerlöf, *J. Am. Chem. Soc.*, **48**, 3046 (1926).

aqueous solutions of acids and salts, the concentrations of which were so adjusted that they all had a freezing-point depression of 4.04°. Acree and co-workers [23] attempted to measure hydrogen-ion concentrations of solutions by means of the hydrogen electrode, but owing to difficulties in the elimination of liquid potentials the attempt was not satisfactory. Harned suggested that the ion activities as defined by G. N. Lewis must play an important rôle in homogeneous catalysis, and in later work he attempted to apply this hypothesis to chemical reactions. Considerable evidence was found that there is a parallelism between ion activities and reaction rates although the results are not entirely conclusive. For example, Harned and Pfanstiel [23] note that the velocity constants for the hydrolysis of ethyl acetate using different concentrations of hydrochloric acid are not all the same but pass through a minimum at about 0.1 *M* hydrochloric acid concentration; this is similar to the behavior of the activity coefficient of the hydrogen ion.

Jones and Lewis [23] in an investigation of the rate of inversion of sucrose agreed with the conclusions of Harned that the activity of the hydrogen ion is the determining factor for the rate of the reaction. It soon became evident, however, that the extension of the substitution of activity for concentration to the other reactants as well as to the hydrogen ion would be necessary, and this was done both by Scatchard [23] and by Moran and Lewis [23] for the sucrose inversion process. A similar study was made for the reaction, hydroxyvaleric acid → valerolactone and water.[23] The results of all this work are not decisive, however, for the different authors disagree as to the mechanism to be selected for a particular reaction and also as to the necessity for including special factors such as the viscosity in the velocity equation.

Recently Brönsted [23] has offered an explanation of the salt effect on the speed of reactions, particularly between ions, based on the postulate that every reaction takes place by the formation of an intermediate complex of extreme instability,[24] whose activity corresponds to its electrical charge which is equal to the sum of the charges of the reactants; the speed of the reaction is assumed proportional to the activities of the reactants and inversely proportional to the activity coefficient of this critical complex. Brönsted shows that chemical reactions between neutral molecules, or between neutral molecules and ions, follow the law of mass action very closely and at most are only slightly sensitive to the addition of a neutral salt; on the other hand reactions between ions are abnormal and the reaction rate depends to a large extent on the total

[24] See Marcelin, *Ann. Physik.*, 3, 120 (1915).

concentration of ions in the solution. If we consider a special reaction such as the decomposition of nitrosotriacetonamine we have,

$$A^\circ \text{ (non-electrolyte)} + OH^- \longrightarrow [A(OH)]^-,$$

where $[A(OH)]^-$ is the critical complex. The velocity of the reaction is then expressed by the equation,

$$v = k[A^\circ][OH^-]\, f_{A^\circ}\, f_{OH^-}\, f_{A(OH)^-}$$

Since the activity coefficients are dependent on the ionic type, $f_0 f_1 / f_1$ becomes f_0 and we have,

$$v = k[A^\circ][OH^-] f_0.$$

Brönsted calls this change in f_0 upon addition of salt the "primary salt effect" which usually increases linearly by 2 to 4 percent when the total salt concentration increases from 0.02 N to 0.10 N. In addition to the primary salt effect Brönsted also postulates the existence of a secondary salt effect due to a change in concentration of one of the reactants, this change in concentration being caused by the shifting of an equilibrium which involves weak electrolytes. For example, if the hydroxyl ion in the above equation is in equilibrium with a weak base, a change in the salt concentration may markedly alter the concentration of the hydroxyl ion and consequently change the reaction rate; the magnitude and direction of the effect depends on the ionic type involved. In the general case, for ideal solutions, where $A + B \rightleftarrows C + OH^-$, the direction of the change in the concentration of the hydroxyl ion with increase in salt concentration depends on whether the sum of the squares of the charges on A and B is greater or less than the sum of the squares of the charges on C and the hydroxyl ion. If greater, the concentration of the hydroxyl ion is decreased; if less, increased. Recent work by Brönsted and King [23] and by Kilpatrick [23] support this concept of the secondary kinetic salt effect. So far as it has been tested Brönsted's hypothesis has been satisfactory, the only criticisms being those of Bjerrum, which are more concerned with a theoretical discussion of the method of developing the velocity equation.

Dry Hydrogen Ion Hypothesis

Rice [25] has put forward a hypothesis which is based on the empirical observation that the temperature coefficient of a reaction is determined largely by the nature of certain "residual molecules" present. The most important of these residual molecules is the unhydrated form of the

[25] Rice, *J. Am. Chem. Soc.*, **45**, 2808 (1923); Rice, Fryling and Wesolowski, *ibid.*, **46**, 2405 (1924).

catalyst. It seems to be a general rule that changing the catalyst changes the value of the temperature coefficient of a reaction; indeed the addition of substances which change the state of combination of the catalyst (such as the addition of neutral salts to weak acids) also changes the value of the temperature coefficient.

It is evident, therefore, that an explanation of the abnormalities of slow reactions may be obtained by postulating that the catalyst exists in two forms, an active form and an inactive form; the active form is present in very minute concentration and its concentration increases rapidly with rise in temperature. We may represent this as follows:

$$H^{+}_{\text{(dissolved)}} + H_2O \rightleftarrows (H,H_2O)^{+}$$

From the temperature coefficients of chemical reactions the heat of the change is approximately 20,000 calories. On the basis of this hypothesis we must arbitrarily define the dry hydrogen ion as having a heat of hydration of 20,000 calories per mole. The dry hydrogen ion in solvents is therefore very different from free hydrogen ions in the gaseous condition which have a heat of hydration of 160,000 calories.

It is assumed, then, that slow reactions exist because one of the reactants (the catalyst) is present in extremely minute amounts and the rate of collision of this and the other reactants is correspondingly small. This cannot, of course, be a complete explanation of the change of reaction rate with temperature because it would follow that all reactions catalyzed by hydrogen ion would have one temperature coefficient, those catalyzed by hydroxyl ion another, and so forth. There is indeed some tendency for this to occur for we have a large number of diverse hydrolytic reactions such as the hydrolysis by dilute hydrochloric acid in aqueous solution, of all fatty acid esters,[26] substituted halogen fatty acid esters,[27] ethyl cyano-acetate and its homologs,[28] ethyl glycollate and its homologs,[29] formyl acetic acid,[30] and lactone formation, all of which have the same temperature coefficient, $k_{35}/k_{25} = 2.4$, within experimental error. The temperature coefficient is not, however, completely independent of the nature of the substrate, because for the reaction between acetone and iodine $k_{35}/k_{25} = 3.1$ and for the hydrolysis of cane sugar $k_{35}/k_{25} = 4.1$, the catalyst for both reactions being dilute aqueous

[26] Ostwald, *J. prakt. Chem.*, **28**, 449 (1883); De Hemptinne, *Z. physik. Chem.*, **13**, 561 (1894); Löwenherz, *ibid.*, **15**, 397 (1894); Harned and Pfanstiel, *J. Am. Chem. Soc.*, **44**, 2193 (1922).
[27] Drushel and Hill, *Am. J. Sci.*, **30**, 72 (1910); Drushel, *ibid.*, **34**, 69 (1912).
[28] Drushel, *Am. J. Sci.*, (a) **33**, 27 (1912); (b) **37**, 514 (1914).
[29] Drushel and Dean, *Am. J. Sci.*, AAQ **34**, 293 (1912); (b) **35**, 486 (1913).
[30] Senter and Ward, *J. Chem. Soc.*, **101**, 2534 (1912).

hydrochloric acid. Since the value of the temperature coefficient is not completely independent of the nature of the substrate it becomes necessary to consider the effect on the temperature coefficient of double compound formation between substrate and solvent. If we consider the equilibrium,

$$A + H_2O \rightleftarrows A,H_2O$$

we may postulate that the substance A has only a small affinity for water so that the equilibrium concentration of A,H_2O is very small; this is probably the condition for most aqueous solutions of organic substances. The substance A,H_2O is referred to as a "residual molecule" and has the property that its concentration is proportional to the equilibrium constant of the reaction; this varies rapidly with the temperature if the heat of the reaction is large. From Kendall's work [31] we may conclude that the heat of formation of simple compounds of the form $AB.CD$ is in general positive because "the tendency to form addition compounds is greatest at low temperatures." If hydration is in general an exothermic process the concentration of A,H_2O will diminish with rise in temperature; further, assuming that the actual mechanism of hydrolysis is a collision between the catalyst and A,H_2O it is evident that hydrolytic reactions in general will have a lower temperature coefficient than is normal for non-hydrolytic reactions. The hydrolysis of cane sugar is an exception to this; this molecule is probably extensively hydrated but we have no information as to the extent of hydration at the point where rupture occurs and no information as to the sign of the heat change.

We may postulate, therefore, that the temperature coefficient of a reaction is determined by the nature of the catalyst; thus the hydrolysis by aqueous sodium hydroxide of ethyl acetate [32] and a number of hydroxy and alkyloxy fatty acid esters [33] give $k_{35}/k_{25} = 1.8$ as compared with 2.4 for the corresponding hydrolysis by hydrochloric acid; similar results have been obtained in the hydrolysis of amides.[34] The relation between the catalyst and the temperature coefficient is also strikingly illustrated by the reaction between acetone and iodine. If hydrochloric acid or any other strong monobasic acid in dilute aqueous solution is used as catalyst, the temperature coefficient k_{35}/k_{25} is 3.08; here, of course, the acid is completely ionized and the hydrogen ion is practically only combined with water; if a dibasic acid such as sulfuric acid is used

[31] Kendall, *J. Am. Chem. Soc.*, **36**, 1241 (1914).
[32] Reicher, *Ann.*, (a) **228**, 251 (1885); (b) **232**, 103 (1886).
[33] Dean, *Am. J. Sci.*, (a) **35**, 605 (1913); (b) **37**, 331 (1914).
[34] Crocker, *J. Chem. Soc.*, **91**, 593 (1917); Kilpi, *Z. physik. Chem.*, **80**, 165 (1912); Peskoff and Meyer, *ibid.*, **82**, 129 (1913).

as catalyst, the hydrogen ion is combined partly with the anion of the acid and partly with the water. The temperature coefficient is 2.89. Finally, if the ionization of the sulfuric acid be still further depressed by 1.69 M ammonium sulfate the temperature coefficient falls to 2.55.

A reaction which is non-hydrolytic and which proceeds in dilute aqueous solution catalyzed by a strong monobasic acid should have a characteristic temperature coefficient $k_{35}/k_{25} = 3.08$; when weaker acids are used the temperature coefficient is lower. For example, the value of k_{35}/k_{25} for sulfuric acid is 2.88 which is about 7 percent lower than the normal value; it is noteworthy that this ratio should hold for any reaction whatsoever which proceeds in dilute aqueous solution because the ratio is governed by the nature of the catalysts in the two cases and is independent of whatever reaction is going on.

Although the temperature coefficient of a chemical reaction is determined mainly by the catalyst, double compound formation by the substrate and consequent formation of a residual molecule may also affect the temperature coefficient. This effect should be usually to diminish the value of the temperature coefficient since the actual reactant is a substrate hydrate formed in small quantity with evolution of heat; its concentration diminishes with rise in temperature.

It may be noted that from the point of view of this hypothesis very fast or very slow reactions should have approximately the same temperature coefficient since this is determined largely by the hydrogen-ion or hydroxyl-ion catalyst whereas from most of the other hypotheses we may conclude that fast reactions have a lower temperature coefficient and a lower value for Q in the Arrhenius equation than slower reactions. Unfortunately our technic for measuring very fast reactions has not advanced very far. Recently Francis [35] has made a study of the relative rates of certain very fast reactions at different temperatures; the actual value of the temperature coefficient for these reactions is unknown but the study made over wide ranges of temperature showed that the coefficients for all the reactions are practically the same. This may mean that these reactions are uncatalyzed and therefore subject only to kinetic effects and not to activation of molecules; or it may mean that the reactions have a common catalyst, possibly the unhydrated hydrogen or hydroxyl ion. Conant and his co-workers [36] have made a study of the reaction between potassium iodide and a great variety of organic chlorides. If we take the reaction rate of the least reactive

[35] Francis, *J. Am. Chem. Soc.*, **48**, 655 (1926).
[36] See Conant, Kirner and Hussey, *J. Am. Chem. Soc.*, **47**, 488 (1925).

substances as unity, the reaction rate of the more reactive chlorides is as high as a million; the temperature coefficients of all these reactions, however, is the same within experimental error and it does not seem possible to explain this on the basis of any hypothesis which postulates active and inactive substrate molecules.

The dry hydrogen ion hypothesis seems up to the present to explain satisfactorily catalysis in acid solution; it does not, however, agree with the results obtained in alkaline solutions or in solutions near the neutral point,[37] and it does not seem possible at present owing to our lack of knowledge of the mechanism of catalysis to decide whether any modification of the original hypothesis will explain catalytic action in alkaline solutions.

Catalysis

As is evident from the foregoing discussion we are very far from a reasonably complete understanding of the nature of catalytic action. It is perhaps to be expected that the hydrogen ion should have unusual properties because from the point of view of atomic structure it holds a unique position among the ions. On the other hand the hydroxyl ion is not markedly different from a number of other ions such as for example the HS^- ion. It seems hardly to be expected that these two ions should have the extraordinary property of catalyzing such a large number of diverse chemical reactions, and it may possibly be significant that hydrogen and hydroxyl ions form the solvent water. It would be interesting to know if hydrogen ion and the amide ion would be catalytically active in liquid ammonia or the CO^+ and Cl^- ions in liquid carbonyl chloride.

The view that the activity of acids in accelerating chemical change is due to the hydrogen ion rests to a large extent on the approximate proportionality between the relative catalyzing powers and the corresponding electrical conductivities of the acids. At the time that this comparison was first instituted it was, however, recognized that the proportionality is by no means an exact one, and Ostwald supposed that the observed deviations were due to secondary factors of relatively small importance. Largely, no doubt, by reason of its simplicity, the theory that the catalytic activity of acids is essentially due to the species of hydrogen ion which conducts the current was accorded a most favorable reception and for many years no serious attempt appears to have been made to challenge its validity. The most serious difficulty which this

[37] Bolin, *Z. anorg. Chem.*, **143**, 201 (1925).

view met was the anomalous effect of neutral salts on the catalytic activity of acids. Usually the presence of a neutral salt, which may or may not have the same anion as the acid, increases the catalytic activity of the acid markedly. Through the researches of Acree, Goldschmidt, Bredig and Snethlage [38] the view gained credence that in such catalytic processes the undissociated molecule of the catalyst possesses specific catalytic activity; Snethlage indeed postulated that the whole phenomenon of neutral salt action may be explained by an assumption of such catalytic action being due to the relatively greater activity of the undissociated molecule.

The remarkable retarding effect of small quantities of water on the catalytic esterification of carboxylic acids in alcohol was also adduced as evidence to support the hypothesis that the undissociated molecule is catalytically active, although indeed Goldschmidt and Udby [39] claimed that their work showed that an alcoholated hydrogen ion is the active catalyst in absolute alcohol solution.

Neutral salt action has been studied mainly in connection with the inversion of cane sugar and the hydrolysis of esters, acids being used as catalysts in both cases. Neutral salt action is independent of the ester used but when cane sugar is hydrolyzed the reaction rate is increased to a much higher degree by a given concentration of salt than in the case of ester hydrolysis. The increase in velocity is quite independent of acid and temperature if a strong monobasic acid is used, but diminishes with temperature for weaker acids. The amount of interest displayed in neutral salt action may be gauged from the list of papers given [40] which includes only work done since 1911.

[38] Acree, *Am. Chem. J.*, **37**, 410 (1907); Goldschmidt, *Z. physik. Chem.*, (a) **70**, 627 (1910); (b) **81**, 30 (1912); Bredig, *Z. Elektrochem.*, **18**, 535 (1912); Snethlage, *ibid.*, **18**, 539 (1912).

[39] Goldschmidt and Udby, *Z. physik. Chem.*, **60**, 728 (1907).

[40] Rivett, *Z. physik. Chem.*, **80**, 537 (1912); Snethlage, *Z. Elektrochem*, **18**, 539 (1912); Bredig, *ibid.*, **18**, 535 (1912); Henderson and Kellog, *J. Am. Chem. Soc.*, **35**, 396 (1913); Falk, *ibid.*, **35**, 601 (1913); Dawson and Powis, *J. Chem. Soc.*, **103**, 2135 (1913); Armstrong and Worley, *Proc. Roy. Soc.*, **87A**, 605 (1912); McBain and Coleman, *J. Chem. Soc.*, **105**, 1517 (1914); Taylor, *Z. Elektrochem.*, **20**, 201 (1914); Fales and Nelson, *J. Am. Chem. Soc.*, **37**, 2769 (1915); Harned, *J. Am. Chem. Soc.*, **37**, 2460 (1915); Ramstedt, *Med. K. Vetensk. Nobelinstitut*, **3**, 1 (1915); Taylor, *J. Am. Chem. Soc.*, **37**, 551 (1915); Lapworth, *J. Chem. Soc.*, **107**, 857 (1915); Dawson and Reiman, *ibid.*, **107**, 1426 (1915); Snethlage, *Z. physik. Chem.*, **90**, 1, 139 (1915); *Ann. Reports*, 1915, p. 19; Holmes and Jones, *J. Am. Chem. Soc.*, **38**, 105 (1916); Harned, *ibid.*, (a) **38**, 1986 (1916); (b) **40**, 1461 (1918); (c) **42**, 1808 (1920); Thomas and Baldwin, *J. Am. Chem. Soc.*, **41**, 1981 (1919); McBain and Kam, *J. Chem. Soc.*, **115**, 1332 (1919); Åkerlöf, *Z. physik. Chem.*, **98**, 260 (1921); Manning, *J. Chem. Soc.*, **120**, 2079 (1921); Rice and Lemkin, *J. Am. Chem. Soc.*, **45**, 1896 (1923).

The simple theory that only the hydrogen ion and the undissociated molecule are catalytically active proved inadequate to explain results, and the tendency now is to assume [41] that there are really a large number of catalytically active particles present. Thus when ethyl acetate is being hydrolyzed by aqueous hydrochloric acid it is assumed that besides the simple hydrogen ion H^+ and the undissociated molecule HCl we have also various double compounds such as $(H,H_2O)^+$, (HCl,H_2O), $(H,CH_3COOC_2H_5)^+$, $(H,CH_3COOH)^+$, etc., all of which are supposed to be catalytically active in varying degree. There is not much possibility of testing this hypothesis because we have perhaps a dozen or so simultaneous reactions occurring in the acid hydrolysis of ethyl acetate and we have no means of measuring the velocities of the different reactions.

The study of catalytic action in non-aqueous solvents has led to the assumption [42] that only the simple hydrogen ion is catalytically active and that compounds containing it have a negligibly small catalytic activity. A great many reactions if performed in very carefully dried organic solvents are greatly retarded by small amounts of water. This behavior on the part of such widely diverse reactions as the transformation of hydrazobenzene into benzidene in alcoholic solution, the decomposition of diazoacetic ester, the bromination of ketones, esterification processes, and the decomposition of oxalic acid by concentrated sulfuric acid indicate that this may be a very general phenomenon and that the true catalyst may in all these cases be the unsolvated hydrogen ion. This postulate that the unsolvated hydrogen ion is the only catalytically active particle is in accord qualitatively with all the facts of homogeneous catalysis. Its quantitative development has not proceeded very far although it has been used [25] as a basis for the quantitative explanation of temperature coefficients. The existence of slow reactions may possibly be determined by an active catalyst present in exceedingly minute amounts so that the number of collisions per second with the other reactants is sufficiently small so that the reaction goes with measurable speed.

Recently the velocity of change of hydroxy acids to lactones [43] in non-aqueous solvents and catalyzed by acids has been studied. Perhaps the most remarkable results obtained were in ether solutions containing small quantities of water. Contrary to results obtained with

[41] See Kendall, *Proc. Nat. Acad. Sci.*, **7**, 56 (1921).

[42] Fitzgerald and Lapworth, *J. Chem. Soc.*, **93**, 2163 (1908); Lapworth, *ibid.*, **93**, 2187 (1908); Dawson, *J. Chem. Soc.*, **99**, 1, (1911); Dawson and Powis, *ibid.*, **105**, 1093 (1914).

[43] Taylor and Close, *J. Phys. Chem.*, **29**, 1085 (1925).

other reactions such as ester catalysis, they found that the less water in ethereal hydrogen chloride, the slower the velocity; the addition of very small quantities of water increases the reaction velocity in ethereal hydrogen chloride tremendously. These solutions, possessing a much lower conductivity than conductivity water, catalyze the reaction a great deal faster than water containing the same concentration of hydrochloric acid. Some of the authors' conclusions may be quoted: "the high velocity of lactone formation in wet ethereal hydrogen chloride as opposed to that in aqueous acid solutions is not due to the ether, since, in dry ether solutions, the reaction velocity is negligibly small. The extreme slowness of the reaction velocity in well dried ethereal hydrogen chloride disposes effectively of any claim that undissociated molecules of the hydrogen chloride have catalytic activity. Nor can the catalytic activity be directly proportional to the acid concentration or to the hydrogen-ion concentration as determined by conductance measurements, since the conductance of the ethereal solutions was a very minute fraction of that of the aqueous solutions, while the reverse is true of the reaction velocity." The authors conclude that their work gives qualitative support to the original hypothesis of Lapworth that it is the non-hydrated hydrogen ion which is responsible for catalytic activity.

Chapter V.

Isomeric Change.

Perhaps the simplest class of chemical reaction is that in which a molecule undergoes an intramolecular change under the influence of a catalyst. A number of examples of this class have now been investigated with some degree of completeness. Lowry and Magson [1] have studied the effect of solvents on the isomeric change of nitrocamphor; Meyer and his co-workers have made extensive studies of keto-enol isomerides mainly with a view of determining the conditions for isolating the two isomerides; in addition a whole host of researches has appeared correlating intramolecular change and the course of a chemical reaction.

Nitrocamphor

The rate of isomeric change is greatly increased by hydroxyl ion but is also sensitive to hydrogen ion and to solid catalysts, glass being the one commonly present. The early work of Lowry [2] and Lowry and Magson [1] enables one to state the conditions which probably govern all reactions of this kind. They found that nitrocamphor when in solution undergoes isomeric change which can be conveniently followed by the polarimeter. It became evident immediately that the rate of change is extraordinarily sensitive to minute traces of accidental impurities; for example, there was a distinct increase in the velocity when piperidine was added to a pure benzene solution in the proportion of one part of piperidine to one hundred million parts of solution. However, by using very highly purified solvents and laboriously repeating experiments until concordant observations were obtained, they found a series of values for the rates of isomeric change in different solvents which they thought were characteristic of the particular solvent. The time taken (in hours) for 99.5 percent of the change for the following four highly purified solvents is: alcohol (100 per cent), 8; acetic acid, 15; ether, 26; benzene, 284. When chloroform was used as solvent the results obtained were so anomalous

[1] Lowry and Magson, *J. Chem. Soc.*, **93**, 107 (1908).
[2] Lowry, *J. Chem. Soc.*, (a) **75**, 220 (1899); (b) **83**, 1316 (1903).

that it was impossible to draw any definite conclusions from them: "Thus in one case a 10 per cent solution in chloroform was kept in a polarimeter tube for a week without the slightest alteration of rotatory power (the actual values of the specific rotation were: 12 minutes, 27.5°; 1 day, 27.5°; 6 days, 27.5°; 7 days, 27.3°) but at the end of this period the change started accidentally (apparently by moving the tube), and then proceeded at a moderate rate until at the end of a fortnight the rotation had fallen to 20°, a value midway between the ordinary initial and final values." The unique behavior of chloroform was finally traced to the presence in it of carbonyl chloride produced by the oxidation of chloroform by air and light:

$$2\,CHCl_3 + O_2 = 2\,COCl_2 + 2\,HCl.$$

"For some months no importance was attached to this observation, but finally it was realized that carbonyl chloride would be a most efficient agent in eliminating aminic impurities, since these would be converted into neutral carbamides, from which the amine could not be recovered even by the most powerful acids."

The efficiency of carbonyl chloride for arresting the progress of isomeric change may be illustrated by the following experiment: a sample of very pure benzene gave a velocity constant of 0.0002, which fell to 0.0000008 when $N/10{,}000$ carbonyl chloride was present and the reaction performed in a silica vessel. Similar results were obtained with other organic solvents such as ether and carbon disulfide so that it became evident that the isomeric change is not a spontaneous process but depends on the presence of impurities. It seems practically certain that further development of the technic of purifying the solvents would result in an immeasurably small velocity.

Experiments with acetyl chloride showed that it is practically as efficient as carbonyl chloride for arresting the progress of isomeric change, so that the action of these substances is almost certainly due to the elimination of basic impurities. The objection to their use is that in the process of elimination, hydrochloric acid is formed which is itself a catalyst for these reactions. Consequently phenyl carbimide was tried but without success, possibly because it reacted with the nitrocamphor. The authors were not able to arrest the change in such "polar" solvents as alcohols and acetic acid, possibly because basic impurities could not be completely removed or because the ionization of the solvent itself was sufficient to catalyze the reaction.

Keto-Enol Isomerism

Much work has been done in keto-enol isomerism. Starting with the now discredited hypothesis of Laar that the mobile hydrogen atom occupied an intermediate position so that there are not two forms present, further investigation showed that not only were the two forms present but that they could be separated and kept without appreciable change if the experiments are performed under "aseptic" conditions, i.e., in absence of catalysts. The first problem to be solved in this connection is a method of analysis of the keto-enol mixture. Since the keto and enol forms have different densities and different refractive indices, physical methods provide a convenient if somewhat rough method of indicating changes in composition; an effective method of analysis must, however, be chemical in nature especially when it is necessary to prove that the pure form of one of the isomers has been prepared. The difficulties of devising such a method are great, because the reactions are sensitive to hydrogen and hydroxyl ions and to the glass walls of the containing vessel; all of the reactions are sensitive to hydroxyl ions, many of them extraordinarily so.

The colorimetric estimation of enols by ferric chloride has been used by Knorr and Schubert [3] to investigate the equilibrium of mesityloxide oxalic esters in different solvents. The method is, however, very limited owing to the catalytic action of the ferric chloride. Claisen's method of estimating enols by extraction with dilute soda is also impractical in most cases, and similarly Michael's method [4] using tertiary bases, since all keto-enol reactions are extremely sensitive to alkali. Molecular rotation [5] and molecular refraction [6] have also been used for analyzing keto-enol mixtures by calculating the value for pure keto and pure enol and then comparing with the observed value; naturally such a result is only approximate.

Knorr [7] has used the refractive index by first isolating the pure keto and pure enol form and determining the refractive index of artificially prepared mixtures of known composition. Equilibrium in solution can be studied in this manner by evaporating off the solvent and determining the refractive index of the residue. His results, however, are not reliable

[3] Knorr and Schubert, *Ber.*, **44**, 2772 (1911); Wislicenus, *Ann.*, **291**, 178 (1896); Meyer, *Ber.*, **45**, 2843 (1912). See also Kaufmann and Wolff, *Ber.*, **57**, 934 (1924).
[4] See Michael and Smith, *Ann.*, **363**, 36 (1908).
[5] Perkin, *J. Chem. Soc.*, **61**, 808 (1892).
[6] Brühl, *J. pr. Chem.*, **50**, 177 (1892); Auwers, *Ber.*, **44**, 3530 (1911).
[7] Knorr, *Ber.*, **44**, 1145 (1911).

(be obtains 2 per cent enol in acetoacetic ester) probably due to the great difficulty of completely excluding catalysts while the necessary operations of his method are being performed.

Hantzsch [8] has used light absorption for estimating keto-enol mixture, a method which is applicable when the keto and enol forms have considerably different absorption spectra.

Analysis of Keto-Enol Mixtures

The most satisfactory method for analyzing these mixtures seems to be the bromine titration method developed by Kurt Meyer.[9] The principle of the method is that all enol forms in alcohol solution react instantly with bromine, whereas the keto forms react comparatively slowly. The first reaction is doubtless the addition of bromine to the double bond followed by splitting out of hydrobromic acid. Apparently, in alcoholic solution the hydrobromic acid does not markedly catalyze the change keto → enol, so that a fairly sharp end point is obtained; however, in many organic solvents, hydrobromic acid is a powerful catalyst so that the titration must be done in the presence of an excess of alcohol. The following method may be used: the keto-enol mixture, whether pure or dissolved in some solvent, is diluted with an excess of alcohol, cooled to about —10° and titrated with a standard solution of bromine in alcohol; the end point is when the color of the bromine persists in the solution and the titer gives at once the amount of enol present.

For this method it is necessary to prepare and standardize new bromine solutions at very frequent intervals, since bromine and alcohol slowly react. This inconvenience may be avoided by titrating with an alcoholic bromine solution of unknown strength until a faint yellow color appears. During this process, bromine adds to the double bond of the enol form, hydrobromic acid splits off, and the enol form is quantitatively converted into the bromoketone, which is estimated by adding potassium iodide and hydrochloric acid, warming slightly and estimating the liberated iodine with thiosulfate. Meyer considers that the action which occurs is replacement of the substituted bromine by iodine, addition of hydriodic acid at the carbonyl group, and splitting out of iodine by the di-iodide.[10]

These methods [11] were tested by using such substances as acetyl di-

[8] Hantzsch, *Ber.*, **43**, 3049 (1910); *idem, ibid.*, **44**, 771 (1911). See also Grossmann, *Z. physik Chem.*, **109**, 305 (1924); Morton and Rosney, *J. Chem. Soc.*, **129**, 706 (1926).

[9] Meyer, *Ann.*, **380**, 212 (1911).

[10] Finkelstein, *Ber.*, **43**, 1528 (1910).

[11] See especially Meyer, *Ber.*, **45**, 2852 (1912).

benzoyl methane, where the two forms are easily isolated and purified. Mixtures of the two forms in alcohol were made up in known proportions and the resulting solutions analyzed, the results being shown in the following table:

Per cent enol taken.	100	45.5	28.04	37.85	25.0	68.7	0
Per cent by analysis	99.8	43.5	28.96	39.8	27.0	71.3	0

Keto-Enol Equilibrium

The methods were then applied to substances like acetoacetic ester which had not at that time been separated into the two forms. Meyer showed that pure liquid acetoacetic ester contains 7.7 per cent enol. The ester was dissolved in a wide variety of solvents and titrated immediately with standard bromine in the same solvent. Provided the titration was done immediately the same result was always obtained independently of the solvent. However, if the solutions were allowed to stand, a new equilibrium characteristic of each solvent was obtained. The velocity of attaining the new equilibrium varied from solvent to solvent and probably depends largely on the presence of traces of impurities. The position of the keto-enol equilibrium point varies widely depending on the solvent used; in general the non-polar organic solvents cause a great increase in the fraction of the enol form. (See

TABLE V

EQUILIBRIUM OF ACETOACETIC ESTER IN DIFFERENT SOLVENTS. TEMPERATURE 18°, EXCEPT AS NOTED.

Solvent	Enol Isomer Per Cent
Water	0.4
Methyl Alcohol (0°)	6.9
Ethyl Alcohol (0°)	12.0
Propyl Alcohol (0°)	12.4
Ether	27.1
Ethyl Acetate	12.9
Acetic Acid	5.7
Acetone	7.3
Chloroform	8.2
Benzene	16.2
Toluene	19.8
Xylene	23.4
Nitrobenzene	10.1
Carbon Disulfide	32.4
Hexane	46.4

Table V.) The usual attempts were made to find an empirical relation between the results and the various physical properties of the solvent, but without success.

Temperature has no measurable effect on the equilibrium point of

the liquid acetoacetic ester. In solution however the fraction of the keto form increases with rise in temperature. In methyl alcohol solution the ester contains 6.9 per cent enol at 0° but only 4.7 per cent enol at 66°; similar results were obtained for the ethyl alcohol solution.

The changes of the equilibrium point with solvent as well as with change in temperature is of course connected with the solubility of the two forms, and Meyer discussed an empirical relation of Dimroth [12] which may be stated:

$$\frac{\text{Equilibrium concentration of enol}}{\text{Equilibrium concentration of keto}} = \frac{\text{Solubility of enol}}{\text{Solubility of keto}} \times C.$$

The constant C is independent of solvent. Meyer devised an interesting experiment to show the small solubility of the enol form in water: a saturated aqueous solution of acetoacetic ester is made and diluted with an equal volume of water. The solution is made alkaline and then acidified with sulfuric acid. An oil is precipitated which gives an intense color with ferric chloride and absorbs bromine instantly. However, when the oil dissolves there is only a very slight coloration with ferric chloride showing that the change to the keto form has taken place. On the other hand, with hexane the solubility of the enol form is so great that it can be extracted from the equilibrium mixture leaving the pure keto form. The ester was extracted three times with double its volume of cooled hexane; the residual ester was freed from dissolved hexane by evaporation in vacuum and on titrating was found to be 98.5 per cent keto.

When acetoacetic ester is freshly distilled the distillate is highly enolized at first but gradually changes to the equilibrium mixture, the rate of change depending on the amount of impurity present. Table VI shows a typical result. In aqueous solution the ester attains equilibrium

TABLE VI

RATE OF CHANGE OF VERY PURE FRESHLY DISTILLED ACETOACETIC ESTER. TEMPERATURE 15°.

Minutes	Enol Isomer Per Cent
0	18.5
60	18.1
960	13.9
2400	10.4
∞	7.9

much more rapidly, the enol falling from 7 per cent to 1 per cent during the course of a minute. The rate of change in water at 0° and 10°

[12] Dimroth, *Ann.*, 377, 127 (1910).

was measured and k_{10}/k_0 was found to be 3; this is of course necessarily only the roughest kind of result. The rate of change in alcohol is moderately fast, the enol percentage in 99.8 per cent alcohol increasing from 7.7 to 10.3 in ten minutes; the presence of water slows up the velocity somewhat. The velocity of change in other solvents varies considerably, depending on the purity of the particular solvent used. The characteristics of the non-polar organic type of solvent are that the velocity of change is extremely sensitive to minute traces of impurities and halogen acids have a very greatly enhanced catalytic activity as compared with their action in water or alcohols. Thus if ordinary acetoacetic ester be added to hexane or carbon disulfide containing a little hydrobromic acid, the ester is found to have reached the new equilibrium in the few seconds required for titration.

Table VII shows the effect of chemical constitution on the keto-enol

TABLE VII

Effect of Structure on Keto-Enol Equilibrium

Pure Liquid 18°	Enol Isomer Per Cent
$CH_3COCH(CH_3)COOC_2H_5$	4.1
$CH_3COCH(CH_3)COOCH_3$	3.2
$CH_3COCHBrCOOC_2H_5$	4.0
$C_6H_5COCH_2COOCH_3$	16.3
$C_6H_5COCH_2COOC_2H_5$	31.9
$CO(CH_2COOC_2H_5)_2$	16.8
$CH_3COCH_2COCH_3$	80.4

equilibrium. These substances are all liquids since solid substances are either pure keto or pure enol. Equilibrium between keto-enol forms occurs only in the pure liquid or dissolved condition and the solid forms are either pure enol or pure keto. The state of the solid form gives no clue to the equilibrium in solution; for example, solid acetyl dibenzoylmethane is pure ketone but in alcohol is 90 per cent enol, while solid oxalacetic ester is pure enol but is only 60 per cent enol in alcohol.

The results of Meyer agree qualitatively with those of Knorr, Rothe and Averbeck,[13] who prepared the two forms by crystallizing at low temperatures and compared artificial mixtures with equilibrium mixtures. Quantitatively the results are not in agreement since Knorr gives acetoacetic ester a 2 per cent enol content. Meyer and Kappelmeier[14] therefore made a careful study of the errors in the bromine titration method and made some improvements in the method. They showed that

[13] Knorr, Rothe and Averbeck, *Ber.*, **44**, 1138 (1911).
[14] Meyer and Kappelmeier, *Ber.*, **44**, 2718 (1911).

the error in estimating the end point was small and that the amount of isomeric change occurring during the titration was negligible; also that freshly prepared alcoholic bromine solution liberates the equivalent amount of iodine from potassium iodide and that bromoacetoacetic ester reacts only slowly with bromine. After considering carefully all possible sources of error they conclude that liquid acetoacetic ester in equilibrium contains certainly over 7 per cent of the enol form.

They then devised a modified method to avoid the main sources of error, namely, the rather long time necessary to titrate with bromine, during which time the equilibrium may be disturbed, and also the difficulty of determining the exact end point: 1 gram (approximately) of ester is dissolved in 30 cc. of alcohol at —7° and freshly prepared cold alcoholic bromine solution (about 0.1 *N*) is added quickly until the solution is yellow; immediately 2 cc. of 10 per cent β-naphthol solution is added, which reacts practically instantaneously with the excess of bromine; all this can easily be done in 15 seconds. Potassium iodide is then added, the solution warmed and titrated with 0.1 *N* thiosulfate. Using this method the authors find that liquid acetoacetic ester contains 7.4 per cent enol.

It should be noted however that sometimes the rate of addition of bromine to the enol form of other keto-enol isomerides is fairly slow at low temperatures; with acetyl dibenzoyl methane it is necessary to make the titration at 10° on account of the slowness of the bromine addition and this higher temperature will naturally increase the error due to enolization during the titration. This behavior indicates that even the bromine addition is catalytic in nature but usually far more sensitive than the keto-enol change. There are some keto-enol isomerides like succinyl succinic ester which have such a high velocity of change even at —7° that the titration method is not successful.

Ferric Chloride Reaction

The ferric chloride reaction of enols has been studied by Meyer[15] who shows, in contradiction to the conclusions of Hantzsch and Desch,[16] that the reaction is fast, and when it appears to be slow the action really is the slow enolization of the keto form followed by a rapid reaction of the enol form and the ferric chloride. Thus if ferric chloride be added to aqueous acetoacetic ester a slight color develops which gradually deepens; if the enolic form be removed by addition of

[15] Meyer, *Ber.*, **44**, 2725 (1911).
[16] Hantzsch and Desch, *Ann.*, **323**, 1 (1902).

a few drops of bromine the color disappears but gradually reappears as the change keto → enol progresses and the process of decolorization may then be repeated. Quantitative experiments in aqueous solution show that the rate of reaction between acetoacetic ester and ferric chloride is proportional to the concentration of the ester but independent of the concentration of ferric chloride, which of course we should expect on the basis of the above hypothesis. In alcoholic solution the ferric chloride catalyzes the keto-enol change very strongly so that quantitative measurements cannot be made; this catalytic effect may really be heterogeneous and due to colloidal ferric oxide.

Benzoyl Acetoacetic Ester

Benzoyl acetoacetic ester,[17] unlike acetoacetic ester, can easily be prepared in the enolic form. The ordinary equilibrium ester is a liquid containing in the case of the methyl ester 17 per cent enol and in the case of the ethyl ester 29 per cent enol. By dissolving in aqueous caustic soda and acidifying with sulfuric acid, all the solutions being below 0°, the free enol separates as an oil which crystallizes on standing. It can be filtered off and dried but slowly changes to the liquid equilibrium mixture, the velocity being of the same order as acetoacetic ester. The effect of solvent is also similar to acetoacetic ester, extensive enolization occurring in such solvents as hexane.

The equilibrium of liquid acetoacetic ester is independent of the temperature, but benzoyl methyl acetate changes slightly to the keto form with rise in temperature; thus at 18° the liquid contains 17 per cent enol but at 100° only 15 per cent.

Malonic Ester

Malonic ester [18] gives no ferric chloride reaction and does not dissolve in aqueous sodium hydroxide. It is consequently of interest to inquire if the sodium salt formed by addition of sodium ethylate to an alcohol solution has the ketonic or the enolic form. The free ester does not react with bromine and is consequently pure ketone. If a strongly cooled alcoholic solution of the sodium salt is acidified with hydrochloric acid and after one minute bromine is added none of the bromine is absorbed, showing the absence of any enol form. Meyer however has succeeded in showing that if the titration with bromine be conducted immediately after acidification, there are considerable quantities (up to 50 per cent) of the enolic form of malonic ester present; this is ex-

[17] Meyer, *Ber.*, **44**, 2729 (1911).
[18] Meyer, *Ber.*, **45**, 2864 (1912).

tremely sensitive to catalysts and very rapidly changes to the keto form. It seems possible that with further improvements in technic the compound $COOC_2H_5CH : C(OH)OC_2H_5$ might be isolated in the free state.

Methane tricarbonic acid ester gives the following equilibrium:

$$(COOC_2H_5)_2CHCOOC_2H_5 \rightleftarrows (COOC_2H_5)_2C : C(OH)OC_2H_5.$$

The crystalline substance melts at 28° and is pure ketone; the melted liquid contains 0.2 per cent enol. By acidifying the alcohol solution Meyer has shown that the sodium salt has the enolic form, since almost 90 per cent of the theoretical amount of bromine is absorbed.

Structure and Keto-Enol Equilibrium

It is interesting to consider the effect of structure on the position of the keto-enol equilibrium point. Compounds of the formula CH_3COR such as acetaldehyde, acetone, acetophenone, etc., do not contain detectable amounts of the enolic form, even in presence of alkali. Compounds with two $-\overset{|}{\underset{R}{C}} : O$ groups attached to a CH_2 group furnish the familiar examples of keto-enol tautomerides and a regular series may be formed showing the effect of constitution on the equilibrium point. The following series is in increasing order of enolizing influence:

$$\begin{array}{cccccccc} CO & CO & CO & CO & CO & CO & CO \\ | & | & | & | & | & | & | \\ OCH_3 & OC_2H_5 & OH & NHC_6H_5 & CH_3 & C_6H_5 & COOR \end{array}$$

The effect of substituting one of the hydrogens of the CH_2 group by alkyl or aryl radicals is usually to increase the fraction of the keto form; thus acetoacetic ester is 7 per cent enolized but ethyl acetoacetic ester is only 3 per cent and benzyl acetoacetic ester 5 per cent enolized. On the other hand substitution of one of the hydrogens of the CH_2 group by active polar groups usually increases the enolic fraction; thus liquid benzoyl acetoacetic ester is 60 per cent enolised.

The equilibrium point of keto-enol isomerides in solvents is, as might be expected, dependent on the concentration. A 42 per cent solution of acetoacetic ester in benzene contains 12 per cent enol, but a 2 per cent solution contains 21 per cent enol. Other solutions show similar behavior, the percentage of enol increasing with the dilution.

Solvent and Keto-Enol Equilibrium

If a number of solvents be considered[19] from the point of view of their effect on the equilibrium constant, C_{enol}/C_{keto}, of acetoacetic

[19] Meyer, *Ber.*, **47**, 826 (1914).

ester, for example, they may be arranged in a series of increasing value of K. It has been found as might be expected that this series is the same for other keto-enol substances, and an interesting semiquantitative relationship may be deduced. Table VIII illustrates this relationship for two substances.

TABLE VIII

EQUILIBRIUM CONSTANT OF ACETOACETIC ESTER AND BENZOYL METHYL ACETATE IN DIFFERENT SOLVENTS.

Solvent	Acetoacetic Ester $K_1 = C_{enol}/C_{keto}$	Benzoyl Methyl Acetate $K_2 = C_{enol}/C_{keto}$	$E = K_2/K_1$
Water	0.004	0.008	2.0
Formic Acid	0.011	0.028	2.5
67% Methyl Alcohol	0.023	0.046	2.0
Acetic Acid	0.061	0.16	2.6
Methyl Alcohol	0.074	0.16	2.2
Acetone	0.08	0.16	2.1
Chloroform	0.089	0.18	2.0
Ethyl Alcohol	0.13	0.32	2.5
Methyl Acetate	0.15	0.33	2.2
Benzene	0.22	0.45	2.1
Toluene	0.26	0.62	2.4
Ether	0.43	0.90	2.1
Carbon Disulfide	0.73	1.6	2.2
Hexane	1.00	2.2	2.2

Meyer has found that each keto-enol substance has a characteristic constant E independent of the solvent. Table IX shows the value of E for different substances when the equilibrium constant of acetoacetic ester is taken as unity. A high value of E indicates of course that the

TABLE IX

VALUES OF E FOR DIFFERENT SUBSTANCES

Substance	E	Substance	E
Acetoacetic Ester	1	Benzoyl Acetone	120
Benzoylacetic Methylester	2.3	Dibenzoyl Methane	350
Benzoylacetic Ethylester	2.6	Acetyl Camphor	8
Acetyl Dibenzoyl Methane	80	Benzoyl Camphor	12
Acetyl Acetone	33	Acetoacetic Anilide	1.4

$$E = K_{substance}/K_{acetoacetic\ ester}$$

compound is much more highly enolized than acetoacetic ester under the same conditions. These tables are very useful because a single measurement for a compound in one solvent enables us to calculate approximately the equilibrium constant in any other solvent. All of these measurements were made at room temperature and in a three per cent solution. It may be noted that the accuracy of the equilibrium

constant K depends upon the extent of enolization as well as on the sensitivity of the compound to catalytic influence. If the compound is largely enolized the error in the equilibrium constant is greatly magnified because $K = \frac{C_{enol}}{C_{keto}}$ and the denominator is a small difference term.

Temperature and Keto-Enol Equilibrium

The variation with temperature [20] of the equilibrium constant of several keto-enol substances was measured in different solvents. The results obtained from acetoacetic ester and benzoyl acetic ester (Table X) are perhaps the most dependable since these substances are comparatively slightly enolized. If we take the value $K_{25}/K_0 = 1.3$ we obtain by substituting in the van't Hoff isochore

TABLE X

Variation of Equilibrium with Temperature in Different Solvents

	Ethyl Alcohol	Toluene	Hexane
Acetoacetic ester K_{25}/K_0	1.25	1.15	1.50
Benzoylacetic ester K_{25}/K_0	1.31	1.14	1.46

$$\text{Keto form} = \text{Enol form} + 1600 \text{ calories.}$$

It is somewhat doubtful whether the differences between different solvents observed by the authors are real or are due to experimental error. This difference for cases like acetyl acetone in hexane is very high because the compound is well over 90 per cent enolized; the percentage of the keto form is obtained by difference and an error of 1 per cent in estimating the enol form may easily change the value of K_{25}/K_0 by 30 to 40 per cent. We may conclude that in solution a rise in temperature increases the fraction of the keto form of all keto-enol substances and that the change is approximately independent of the substance and of the solvent.

Meyer and Willson, however, conclude that they can distinguish between the heat effects in different solvents, and give the following values for the change keto→enol: alcohol, 2000 calories; toluene, 1000 calories; hexane, 2700 calories.

Isolation of Keto-Enol Isomers

Perhaps the most interesting part of the work on keto-enol isomers is the later stage when the technic had been sufficiently improved so that

[20] Meyer and Willson, *Ber.*, 47, 832 (1914).

the two isomers even if very reactive could be prepared and kept separately. Meyer and Willson [21] made a careful study of the cause of the difference of the result of Knorr, Rothe and Averbeck,[22] who conclude that ordinary acetoacetic ester contains only 2 per cent of enol. In order to clear up the matter they prepared the keto form of the ester by two methods and measured its physical properties. They used a device, suggested privately by Dieckmann, of adding a trace of oxalic acid to the ester and to the solvents used; this removed traces of alkaline impurities which greatly hasten the rate of tautomeric change.

By shaking 5 cc. of acetoacetic ester with two 20 cc. portions of petrol (b.p. 35°), separating the ester and freeing it from dissolved petrol by evaporating in vacuum, the enol content fell to about 1 to 2 per cent.

The keto form was also obtained by Knorr's method of freezing from petrol at —80° and evaporating off the residual petrol in vacuum; the keto form obtained in this way contained less than 1 per cent of enol. By comparison of the physical constants and the results of titrations they showed that the results of Knorr, Rothe and Averbeck were incorrect, probably due to isomerization while measurements were being made.

The latest work [23] has shown that it is quite practicable to prepare both forms of keto-enol substances by distillation methods. The principle of the method lies in the complete exclusion of catalysts, the whole operation being conducted under "aseptic" conditions. The authors show that in the vapor state no isomerization occurs; the condensate on the walls of the column and on the neck of the flask loses the more volatile enol form as vapor, but the residue rapidly isomerizes to the equilibrium form, so that the whole distillate is highly enolized and is stable if preserved in a quartz receiver; a ketone rich residue is left in the distillation flask.

Various mixtures of the keto and enol forms of acetoacetic ester were distilled, precautions being taken to prevent condensation on the walls of the apparatus. It was found that the percentage of enol in the distillate was the same as the original mixture. Similar results as above were obtained with methyl benzoyl acetate.

There are two methods of fractionating keto-enol which give different results. In glass apparatus without excluding catalysts the ester

[21] Meyer and Willson, *Ber.*, **47**, 837 (1914).
[22] Knorr, Rothe and Averbeck, *Ber.*, **44**, 1138 (1911).
[23] Meyer and Schoeller, *Ber.*, **53**, 1410 (1920); Meyer and Hopff, *ibid.*, **54**, 579 (1921).

becomes highly enolized (80-90%). If distilled in quartz apparatus under "aseptic" conditions (freedom from catalysts) no tautomeric change occurs and the enol form distills over and the keto form is left. By this method the pure keto form can be obtained in one operation.

The present practice is to use a combination of the two distillation methods for preparation of the pure enol form. The equilibrium mixture is first highly enolized by distillation in glass apparatus and the distillate is then transferred to a quartz apparatus which yields the pure enol form. In these experiments they used acetoacetic ester and acetyl acetone; a trace of phthalic acid (Dieckmann) was used as negative catalyst. They did not succeed in getting the pure keto form of acetyl acetone, since the residue in the flask becomes slightly colored and reverts with extraordinary ease to the equilibrium mixture.

Catalysis in Keto-Enol Change

Rumeau [24] has investigated the action of many accelerators and stabilizers (about 0.1%) on pure liquid acetoacetic ester. The method used was to distill the ester, thus obtaining a distillate containing 50 to 80 per cent enol; the various substances were added to this distillate and the rate of change to the equilibrium concentration of 7 per cent was measured by the refractometer or by titration. Soft glass rapidly brings the ester to equilibrium, whereas it can be preserved in pyrex or quartz for considerable periods. For example, an ester of 52 per cent enol content contained 7 per cent enol after 20 minutes in ordinary glass, 30 per cent enol after 4 hours in quartz and 52 per cent enol after 4 hours in pyrex.

A number of substances were found which powerfully catalyze the change. It is surprising to note that bromine is one of these substances, a minute trace bringing the ester to equilibrium in a few seconds. Iodine, however, has no such effect. Above everything, alkalis show the most energetic effect, and any appreciable trace brings about equilibrium instantaneously. Strong mineral acids are also strongly catalytic but much less so than alkalis. A number of phenolic substances were tried and some were found to be accelerators, some indifferent and some inhibitors. The results leave the suspicion that they are due rather to accidental impurities in the phenolic substances than to any specific properties of these, and this may also be the case in certain other results obtained in the work. For example, oxalacetic ester was found to be an energetic stabilizer, but if the ester was distilled the residue in

[24] Rumeau, *Bull. Soc. chim.*, **35**, 762 (1924).

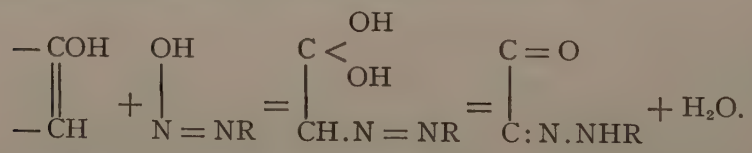
the flask was an energetic accelerator of the reaction. Contrary to Dieckmann, phthalic acid was found to exercise no stabilizing action.

Reactions of Keto-Enol Isomers

Two theories [25] are used to explain the mechanism of the reaction of keto-enol isomerides. The first, which may be called the substitution theory, states that a substance can yield only derivatives similar to its own constitution; when an enol derivative by reaction yields a keto derivative, what really happens is that the enol forms first changes to the keto form and then reacts. The second theory, which may be called the addition theory, states that a keto form need not become transformed to the enol form in order to yield an enolic derivative; the keto form may add the reagent, split out a part of the molecule and form the enolic derivative directly. Meyer considers a number of types of reaction in the endeavor to answer the question "Which of the two forms reacts?"

It seems fairly evident that the halogens, bromine, for example, react only with the enolic form and then split out hydrobromic acid yielding a bromoketone.

Alkylation of keto-enol substances has been much used [26] to determine the composition of the original substance, but Meyer states that in general this is not possible and quotes the example of anthrahydroquinone,[27] in which a pure enol form on alkylation yields a derivative of a keto form. He therefore favors the Michael-Nef formulation of addition of the alkyl halide to the double bond. Wislicenus himself assumes that the sodium combines with the halide and the alkyl radical combines with the unsaturated residue. Meyer regards the coupling with diazo compounds to be represented as follows: [28]

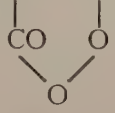


Many keto-enol substances react with aldehydes and the condensation is usually followed by successive reactions involving splitting out of part of the molecule. The reaction between mesityloxide oxalic ester and benzaldehyde enables us to distinguish whether the enol form or

[25] Meyer, *Ann.*, **398**, 49 (1913).
[26] Wislicenus, *Ahrens Sammlung*, **2**, 187 (1898).
[27] Meyer, *Ann.*, **379**, 47 (1911).
[28] See also Dimroth, *Ber.*, **40**, 2404 (1907).

keto form reacts. The condensation is represented by the following equation:

$$(CH_3)_2 : CHCOCH : C(OH)COOCH_3 + C_6H_5CHO$$
$$= (CH_3)_2C : CHCOCH - CHC_6H_5 + CH_3OH.$$



Only the enolic form of the mesityloxide oxalic ester reacts with the benzaldehyde; the resulting lactone appears in the keto form, so that we have an enol form reacting and the keto form produced. Meyer holds it as very probable that for all tautomeric compounds, even substances like acetaldehyde and acetone, the enol form condenses; these condensations take place in presence of substances like hydrochloric acid, caustic soda, piperidine, etc., which increase the rate of isomerization.

The lactone was prepared by dissolving 1 gram of mesityloxide oxalic ester in 4 grams of benzaldehyde in the presence of a trace of piperidine. When the keto ester was used it was recovered unchanged after four days but the enol ester reacted rapidly.

The keto form of the lactone is the stable form. If the enolic form is dissolved in benzaldehyde in the presence of piperidine, even after three days an appreciable quantity of the enolic form has not been converted to the keto form. This suggests that the keto form of the lactone is the primary product of the condensation.

Halogenation of Keto-Enol Isomers

The mechanism of halogenation of keto-enol substances has been extensively investigated. For example it was desired to determine whether the bromination of malonic acid occurs in two stages. Two experiments were performed side by side in which bromine was added to aqueous malonic acid and the time noted for decoloration to take place. In one experiment the whole of the bromine was added at once, whereas in the second experiment the bromine was added in ten portions, each portion being added as soon as the previous portion was used up. The time taken for each experiment was the same within experimental error, showing that the rate of the reaction is independent of the bromine concentration; consequently we have a slow initial reaction followed by an instantaneous bromination. This reaction goes at the same rate in bright sunlight as in the dark so that evidently the initial change is not affected by light.

The chlorination of acetic acid is extremely sensitive to light so that it seems probable that we have here direct chlorination similar to the chlorination of the paraffins. This conclusion may not be correct, for Lapworth [29] has shown that when acetic acid is free from water the addition of halogens is strongly catalyzed by acids similarly to keto-enol substances. In this paper Lapworth also gives an account of a quantitative investigation of the action of bromine on acetone in dilute aqueous solution. In neutral solution the action is exceedingly slow, but is catalyzed by acids, the resulting accelerations being approximately proportional to the strength of the acid. Only one hydrogen of the acetone is substituted, the stoichiometric equation representing the change being:

$$CH_3COCH_3 + Br_2 = CH_3COCH_2Br + HBr.$$

The reaction is therefore catalytic. The rate of the reaction is proportional to the concentration of acetone and to the concentration of acid but is quite independent of the concentration of bromine. Lapworth suggested the hypothesis that the bromination of the acetone is best regarded as the result of a slow reversible change effected in the acetone by the hydrogen ions, followed by an almost instantaneous bromination of the product, a change which is not appreciably reversible. The intermediate form is perhaps the enolic form of the ketone.

$$CH_3COCH_3 + H^+ \rightleftarrows CH_3C(OH) : CH_2 + H^+,$$
$$CH_3C(OH) : CH_2 + Br_2 = CH_3CBr(OH)CH_2Br,$$
$$CH_3CBr(OH)CH_2Br = CH_3COCH_2Br + HBr.$$

Dawson [30] and his co-workers, using iodine instead of bromine, repeated and extended Lapworth's work and endorsed the keto-enol transformation theory.

If this viewpoint is right, it becomes evident at once that the rate of addition of chlorine and iodine should be exactly the same as bromine. The results of the early work showed that the rates of addition of bromine and iodine were approximately the same but chlorine was anomalous. However, in a recent investigation [31] these differences were shown to be due to experimental error, the rates of the three halogens being the same within one per cent. We may make a further test of the hypothesis by replacing the acetone by one of its homologs;

[29] Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).
[30] Dawson and Leslie, *J. Chem. Soc.*, **96**, 1860 (1909); Dawson and Wheatley, *ibid.*, **98**, 2048 (1910).
[31] Rice and Fryling, *J. Am. Chem. Soc.*, **47**, 379 (1925).

since the replacement in keto-enol isomers of mobile hydrogen atoms favors the keto form we may assume that this replacement diminishes the velocity of the change keto→enol, consequently the homologs of acetone should react more slowly than acetone itself. This however is not the case, for many of the higher ketones react faster than acetone. Thus the velocity constants for acetone, methyl ethyl ketone and diethyl ketone are 17.1, 20.9 and 17.1 respectively; these ketones were purified with great care so that it is unlikely that the differences are due to impurities. This result casts some doubt on the hypothesis that the slow preliminary change is enolization of the ketone. The primary change in the bromination of the ketone form of keto-enol substances is undoubtedly a slow change of the ketone form to some activated condition under the influence of hydrogen ions followed by immediate bromination. Further support for this idea is obtained from the experiments of Dawson and Powis.[32] They devised a very delicate test for the presence of any enolic isomer in ordinary acetone, and found no measurable change in conductivity on adding iodine to a neutral solution of acetone, which suggests that there is no appreciable amount of the enolic isomer present. On the other hand Evans and Nicoll [33] conclude that in alkaline solution acetone is largely enolized. They have found that a maximum of 27 per cent of the acetone can exist in the enolic form.

Geometric Isomers

The transformation of geometric isomers provides an interesting example of this type of change which has been carefully studied recently for the transformation of maleic into fumaric acid.[34] Although the early work is largely contradictory and polemical in character it seems clear that the change is catalyzed both by hydrogen ion and hydroxyl ion; that under certain conditions malic acid is formed, but whether as an intermediate product or a side reaction is not certain. Weiss and Downs cite an experiment in which maleic acid was heated at 140° without the presence of solvent; the main reaction that occurs is the formation of fumaric acid but at the same time some of the maleic acid becomes dehydrated to give the anhydride and the water formed reacts with unchanged maleic acid to give malic acid. It is possible therefore that under these conditions malic acid is an intermediate

[32] Dawson and Powis, *J. Chem. Soc.*, **101**, 1503 (1912).
[33] Evans and Nicoll, *J. Am. Chem. Soc.*, **47**, 2789 (1925); see also Witzemann, *ibid.*, **39**, 2657 (1917).
[34] Weiss and Downs, *J. Am. Chem. Soc.*, **44**, 1118 (1922).

product, especially as Weiss and Downs have shown that in water solution at 140° an equilibrium exists between malic and fumaric acids; thus an aqueous solution of either maleic or fumaric acid at 140° gave an equilibrium solution of malic acid and fumaric acid.

The chemistry of maleic and fumaric acids is however far from clear. If an aqueous solution of maleic acid is exposed to light [35] it is transformed to fumaric acid if traces of bromine or iodine are present, but chlorine does not bring about the change. Presumably there is first activation of the halogen by the light, a collision of the activated halogen with a molecule of maleic acid, followed by the transformation. However even in dilute solution one would expect addition of halogen to the double bond at the moment of transformation. Even when conditions are such that the halogen adds to the double bond the results are just as mysterious. On the basis of the Le Bel-van't Hoff theory, bromination of maleic acid should give *meso*-dibromosuccinic acid, and bromination of fumaric acid should give the racemic form; actually the main products are the opposite to what is expected, and it is immaterial whether chlorine or bromine is used. On the other hand, when the halogenation [36] is conducted in a solution of the neutral salts of the acids the chlorination of both salts and the bromination of sodium maleate occurs normally, but bromination of sodium fumarate gives only 10 per cent of the expected *iso*-dibrom derivative.

Oxidation of the acids by permanganate in neutral solution also gives results exactly as predicted, namely, *meso*-tartaric acid from maleic acid and the racemic acid from fumaric acid. These results are typical and it is evident that these reactions of fumaric and maleic acids have much in common with the Walden inversion. The complicated and contradictory nature of the results obtained make it almost impossible to formulate any reasonably satisfactory theory. It seems probable that anomalous results may in many cases be ascribed to heterogeneous catalysis causing special orientations by adsorption on a surface. Recently a paper has appeared [37] discussing these phenomena from the point of view of the electron theory of valency.

The transformation of maleic acid into fumaric acid in aqueous

[35] Wislicenus, *Ber.*, **29**, 1080 (1896).

[36] The solution must be kept saturated with the corresponding sodium halide to prevent hydrolysis of the halogen and formation of halogen malic acids (COOH-CHX-CHOH-COOH); with excess of halogen ion present, dihalogen succinic acid (COOH-CHX-CHX-COOH) salts are produced.

[37] Terry and Eichelberger, *J. Am. Chem. Soc.*, **47**, 1067 (1925); Freundlich and Schikorr, *Kolloidchemische Beihefte*, **22**, 1 (1926).

solution in presence of catalysts has been studied.[38] The rate of the reaction was found to be proportional to the square of the concentration of maleic acid and to the first power of the concentration of catalyst. The mechanism of the change may therefore be represented in some such manner as the following:

$$2\ \begin{matrix}\mathrm{CHCOOH}\\ \|\\ \mathrm{CHCOOH}\end{matrix} \rightleftarrows \left\{\begin{matrix}\mathrm{CHCOOH}\\ \|\\ \mathrm{CHCOOH}\end{matrix}\right\}_2$$

This first change is a very rapid reaction and the double molecules of maleic acid are supposed to be present in very small concentration. The second reaction is the slow measured change:

$$\left\{\begin{matrix}\mathrm{CHCOOH}\\ \|\\ \mathrm{CHCOOH}\end{matrix}\right\}_2 + \mathrm{H^+} = 2\ \begin{matrix}\mathrm{CHCOOH}\\ \|\\ \mathrm{HOOCCH}\end{matrix} + \mathrm{H^+}$$

One of the catalysts used was potassium thiocyanate. This is somewhat puzzling because it seems hard to understand why this substance should have any unusual power to effect the transformation of maleic acid. Meerwein and Weber [39] have considered this ability of different catalysts to cause the transformation of sterio-isomeric ethylenic compounds, and conclude that it depends on their power of activating the double bond. All substances which have the power of addition at the double bond should also catalytically accelerate the transformation of sterio-isomeric ethylenic compounds to a greater or less degree. The authors find support for this hypothesis in the observation that metallic potassium, which has the known power of addition at the ethylene linking, effects the transformation of methyl maleate into methyl fumarate in the presence of dry ether; the potassium is not affected in any way.

Terry and Eichelberger postulate a different mechanism for the reaction: The first change is saturation of one of the carboxyl groups of maleic acid by another molecule of maleic acid; this reaction is

$$2\ \begin{matrix}\mathrm{CHCOOH}\\ \|\\ \mathrm{CHCOOH}\end{matrix} \rightleftarrows \begin{matrix}\mathrm{CHCOOH}\\ \|\\ \mathrm{CHCOOH,(CHCOOH)_2}\end{matrix}$$

very fast and the double molecules are present in very small concentration. The second reaction is addition of catalyst to the associated maleic acid; this is also a rapid reaction and only a small proportion of

[38] Terry and Eichelberger, *ibid.*, 47, 1402 (1925).
[39] Meerwein and Weber, *Ber.*, 58, 1266 (1925).

the associated maleic acid is converted into the new complex, which then slowly becomes activated into an electromer:

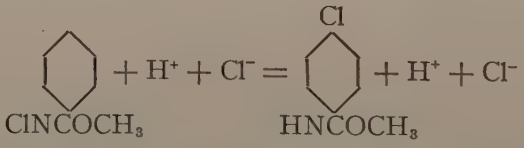
$$\begin{array}{l} \mathrm{CHCOOH} \\ \| \\ \mathrm{CHCOOH,(CHCOOH)_2} \end{array} + \mathrm{H^+} = \begin{array}{l} \mathrm{CHCOOH,H^+} \\ \| \\ \mathrm{CHCOOH,(CHCOOH)_2} \end{array}$$

$$\begin{array}{l} \mathrm{CHCOOH,H^+} \\ \| \\ \mathrm{CHCOOH,(CHCOOH)_2} \end{array} = \begin{array}{l} + \mathrm{CHCOOH,H^+} \\ | \\ - \mathrm{CHCOOH,(CHCOOH)_2} \end{array}$$

This formation of an active form of the double bond is the slow measured reaction and is followed by transmutation to fumaric acid and dissociation of the complex, both rapid reactions. It seems evident that the transformation of geometric and optical isomers is more complicated than the simple keto-enol isomerism; possibly this may be due to heterogeneous catalysis occurring in many of the examples. Terry and Eichelberger, however, tested for surface action in the maleic-fumaric acid transformation and found it absent. We may note that the experiments of Freundlich and Schikorr on the effect of colloidal sulfur in effecting the transformation of maleic acid into fumaric acid indicate that the reaction can occur through some obscure mechanism of a heterogeneous nature.

Acetylchloroaminobenzene

In some examples of isomeric change we have interchange of two atoms or groups in a molecule. This occurs in the conversion of acetylchloroaminobenzene to *p*-chloroacetanilide under the influence of hydrogen and chloride ions:[40]



Presumably the reaction is trimolecular and consists of simultaneous collision of a hydrogen ion at the amino group and a chloride ion at the *para* position. That it is not merely an intramolecular change seems clear not only from the dependence of the rate on the chloride-ion concentration but also from the fact that the change is not catalyzed by sulfuric acid. Perhaps the simplest explanation is that the hydrogen ion

[40] Blanksma, *Rec. trav. chim.*, (a) **21**, 366 (1902); (b) **22**, 290 (1903); Orton and Jones, *J. Chem. Soc.*, **95**, 1456 (1909); Acree and Johnson, *Am. Chem. J.*, **38**, 274 (1907); Harned, *J. Am. Chem. Soc.*, **40**, 1471 (1918).

collides with the amino group and replaces the chlorine which gives up its electron forming the chloride ion; simultaneously a chloride ion already existing in the solution collides with the *para* hydrogen atom and replaces it, gaining an electron and forming a hydrogen ion in the solution. The mechanisms suggested up to the present for the reaction usually postulate combination between the acetylchloroaminobenzene and the hydrogen and chloride ions, followed by rearrangement of the complex compound; it seems however somewhat unlikely that such compound formation would occur.

On the basis that the reaction is trimolecular we may note that if hydrobromic acid is used as catalyst we would expect to obtain *p*-bromoacetanilide from acetylchloroaminobenzene, and this has been verified experimentally. On the other hand acetylbromoaminobenzene and hydrochloric acid should yield *p*-chloroacetanilide but Acree and Johnson state that *p*-bromoacetanilide is the product. No mention of yields is made and it may be that the hydrobromic acid called for by theory is actually formed and then reacts with acetylbromoaminobenzene still in solution. Hydrobromic acid is a much stronger catalyst than hydrochloric acid. Whatever mechanism is ascribed to this reaction it is probable that a similar mechanism will describe other examples of isomeric change involving the interchange of two groups or atoms in a molecule, such as the Beckmann rearrangement, the rearrangement of 2-hydroxy-3-phenylindazole [41] and the rearrangement of derivatives of phenylnitramine to derivatives of nitraniline.

[41] Auwers and Sondheimer, *Ber.*, **29**, 1255 (1896).

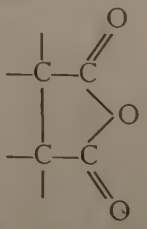
Chapter VI.

Hydrolytic Reactions.

No class of reactions has been so completely investigated as those in which an organic compound reacts with water. A great mass of data exists in connection with the hydrolysis of esters, sugars and amides, and reports of new investigations are continually appearing.

Hydration of Acid Anhydrides

Perhaps the simplest type of reaction involving water is the hydration of acid anhydrides,[1] which had early been shown to proceed with measurable speed. Various methods have been used to follow the reaction. Menschutkin and Vasilieff and also Lumiere and Barbier used the reaction between aniline and acetic anhydride to form acetanilide (which is exceedingly rapid) for determining the extent of hydration of acetic anhydride. This reaction liberates one molecule of acetic acid from one molecule of acetic anhydride, whereas the hydrolysis forms two molecules of acetic acid from one molecule of anhydride. It is evident therefore that a titration with alkali after addition of aniline can be used to give a measure of the extent of the reaction. This early work was only rough and it was not until Rivett and Sidgwick applied the change in conductivity with time to the measurement of a number of acid anhydrides that quantitative measurements became available for aqueous solutions. By conducting the reaction in an electrolytic cell and measuring the conductivity from time to time it is evidently easy to obtain a measure of the rate of the reaction. The authors measured the rate of hydration of acetic anhydride and a number of the anhydrides containing the ring,



[1] Menschutkin and Vasilieff, *J. Russ. Chem. Soc.*, **21**, 192 (1889); Benrath, *Z. physik. Chem.*, **67**, 501 (1909); Lumiere and Barbier, *Bull. Soc. chim.*, **35**, 625 (1906); Rivett and Sidgwick, *J. Chem. Soc.*, **97**, 733, 1677 (1910).

The relative velocity constants are shown in round numbers in Table XI; the absolute velocity constant of acetic anhydride is 0.0026.

TABLE XI

RELATIVE RATES OF HYDRATION OF ACID ANHYDRIDES

Anhydride	*k*
Acetic	1
Succinic	1
Methyl Succinic	1.4
Itaconic (Methylene Succinic)	1.1
Maleic	10
Citraconic (Methyl Maleic)	6.6
Phthalic	4.0

Since good constants were obtained without taking into account the acid formed from the anhydride, Rivett and Sidgwick concluded that the reaction is not catalyzed by hydrogen ion and that the mechanism of hydration of an acid anhydride is quite different from the hydrolysis of an ester or an amide.

Orton and Jones [2] also studied the rate of hydration of acetic anhydride in aqueous solution and in solutions of glacial acetic acid, acetic anhydride, and acetone containing small quantities of water. They found that the velocity constant in acetic anhydride as the solvent was by far the smallest, so that it is a curiously unfavorable medium for its own reaction with water. In those solvents containing but little water, acids are powerful catalysts, but the catalytic effect diminishes as the proportion of water is increased, in agreement with the results of other workers. Alkalis are exceedingly powerful catalysts and even in minute concentration accelerate the hydrolysis so that it is too fast for measurement. It is interesting to note that the velocity constant diminishes slightly as the concentration of acetic anhydride increases; this is the opposite to the observation of Ostwald,[3] but it must be remembered that his experiments were done in presence of 0.66 *N* hydrochloric acid. It would be interesting to repeat these in presence of a weak solution of the catalyst. The experimental procedure developed by these authors was to stop the reaction by the addition of an excess of 2,4 dichloroaniline which combines with the acetic anhydride to form the anilide at a very rapid rate. This is extracted, converted to the chloroamine $C_6H_3Cl_2NClAc$ by bleaching powder and the chloroamine can then be estimated volumetrically by treating with potassium iodide and titrating the liberated iodine.

[2] Orton and Jones, *J. Chem. Soc.*, 101, 1708 (1912).
[3] Ostwald, *J. pr. Chem.*, 28, 449 (1883).

Wilsdon and Sidgwick [4] also made some measurements on the hydration of acid anhydrides using the conductivity method. A summary of their results is given in Table XII from which it will be seen that the temperature coefficients of all these reactions is approximately the same. From their results we obtain $Q = 11{,}100$ whence $k_{35}/k_{25} = 1.84$. This low value suggests hydroxyl-ion catalysis especially when

TABLE XII

RATE OF HYDRATION OF ACID ANHYDRIDES

Anhydride	$k_{25} \times 10^4$	$k_{15} \times 10^4$	k_{25}/k_{15}
Acetic	12.6	8.02	1.58
Propionic	6.20	4.19	1.48
Camphoric	1.58	0.975	1.64

we consider the extreme susceptibility of the reactions to alkali. It would be interesting to repeat some of the work using quartz vessels and taking precautions to eliminate all traces of aminic impurities. A review of the work done suggests that the mechanism of hydration is very similar to ester hydrolysis except that the anhydrides are much more sensitive to hydroxyl ion and much less sensitive to hydrogen ion; consequently we may provisionally postulate some such mechanism as the following:

$$(CH_3CO)_2O + H_2O \rightleftarrows (CH_3CO)_2O,H_2O$$
$$(CH_3CO)_2O,H_2O + OH^- = 2\ CH_3COOH + OH^-$$

The first reaction is very fast and the equilibrium point is largely to the left.

Wilsdon and Sidgwick examined the rate of hydration of monochloroacetic acid but found it to be far too great for even approximate measurement; they estimate about 1.5 seconds as the half-life period. They also tried to examine quantitatively the effect of alkali and concluded that the reaction went approximately 10,000 times faster in presence of 0.05 *N* alkali than in pure water.

Boeseken and Verkade [5] have also measured the rates of hydration of various aliphatic anhydrides and have considered the possible connection between the rate of hydration and the dissociation constant of the acid, since these two show a tendency to rise and fall together.

[4] Wilsdon and Sidgwick, *J. Chem. Soc.*, (a) **103**, 1959 (1913); (b) **107**, 679 (1915).

[5] Boeseken and Verkade, *Proc. K. Acad. Wetensch. Amsterdam*, **16**, 718 (1914).

Skrabal[6] has measured the rate of hydration of acetic anhydride by taking advantage of the fact that hydrogen ion liberates iodine from a mixture of sodium iodide and sodium iodate and the iodine can be determined by thiosulfate.

Lactones

The formations of lactones, in which α-, γ- or δ-hydroxy acid loses a molecule of water, may be regarded as a converse process to the hydration of anhydrides. The reaction is catalyzed by hydrogen ions, and in moderately dilute aqueous solution at equilibrium usually contains over 90 per cent of lactone; since the acidity of the solution diminishes the progress of the reaction is easily followed by titration. A considerable amount of study[7] has been given to these reactions but as is usual with this type of reaction the mechanism of the change is far from being understood. The earlier workers showed that the rate was approximately proportional to the hydrogen-ion concentration although over wide ranges deviations showed up corresponding to those in ester catalysis. The anomalous neutral salt effect is present in lactone catalysis. Taylor and Close in their first paper endeavor to explain their results on the basis of the dual theory of acid catalysis, but in their second paper they show that this theory is incorrect.

Garrett and Lewis studied the mechanism of the formation of valerolactone; they measured the rates of the reaction at 25° and 35° in aqueous solution in presence of various concentrations of hydrochloric acid; additional experiments were made in presence of sucrose, potassium chloride and lithium chloride, as water-displacing agents. The study was made from the thermodynamic point of view using activities as far as possible instead of concentration terms, and correcting for the influence of the viscosity of the solutions on the velocity. The activities of the ions were obtained from e. m. f. measurements and the activity of the sucrose was obtained by expressing the concentration in moles per unit of free or available water present, which in this case is much less than the total water present. In the case of an unsolvated or slightly solvated solute present alone in a solvent, its activity was taken as identical with its concentration; when a second heavily hydrated solute is also present this cannot be done unless the unsolvated solute

[6] Skrabal, *Monatsh.*, **43**, 493 (1923).

[7] Henry, *Z. physik. Chem.*, **10**, 96 (1892); Taylor and Close, *J. Am. Chem. Soc.*, **39**, 422 (1917); Kailan and Neumann, *Z. physik. Chem.*, **101**, 63 (1922); Garrett and Lewis, *J. Am. Chem. Soc.*, **45**, 1090 (1923); Taylor and Close, *J. Phys. Chem.*, **29**, 1085 (1925).

dissolves in the water of hydration of the secondary, heavily-hydrated solute. In some cases the primary unsolvated solute dissolves in the water of hydration of the secondary heavily-hydrated solute, whereas in other cases no such solution occurs. The actual decision here was made by testing which alternative assumption led to values of k independent of environment. On the basis that the reaction actually measured is bimolecular, namely, hydroxyvaleric acid and hydrogen ion give a momentary complex or the resultants direct, a characteristic constant is obtained dependent only on the temperature. It may be noted however as an interesting empirical observation that if the velocity constant be calculated as the rate of the reaction when the concentrations are one mole of hydroxyvaleric acid and one mole of hydrochloric acid per liter (no corrections of any kind being made), the temperature coefficient for all the different conditions is the same, namely, 2.3 for k_{35}/k_{25} within experimental error; it hardly seems possible that this result is without theoretical significance.

The second paper of Taylor and Close consists of an extensive study of lactone formation from hydroxyvaleric acid and *o*-hydroxymethylbenzoic acid in both aqueous and non-aqueous solvents. The velocity of the reaction in aqueous solution is only approximately proportional to the hydrogen ion as determined by conductivity measurements, for both hydrochloric acid and chloroacetic acid. The velocity increases more quickly than the hydrogen-ion concentration as determined by conductance methods, so that the conversion of hydroxyvaleric acid to the lactone is similar in this respect to the other examples of acid catalysis in which the same disproportionality is found. The anomalous neutral salt effect appears also in lactone formation, the reaction rate increasing markedly on addition of potassium chloride to solutions catalyzed by hydrochloric acid; when the reaction is catalyzed by chloroacetic acid the addition of sodium acetate first diminishes and then increases the rate. The effect of 1 N potassium chloride, calcium chloride and magnesium chloride is to increase the catalyic effect of hydrochloric acid, the magnitude of the change increasing in the order named; it is noteworthy that this order is the same as that observed by Washburn and others for the relative hydration values of the cations. The increase in velocity caused by the neutral salt is independent of the temperature, or in other words the temperature coefficient of the reaction is independent of the presence of neutral salts.

The most interesting and unexpected results were obtained, however, when the solvent was varied. Kailan and Neumann had found

that the rate of lactone formation in absolute alcohol is very much faster than in water and that the addition of water greatly slows up the reaction velocity, which falls rapidly and passes through a minimum before the aqueous solution is reached. This inhibitive effect of the water in alcoholic solution is also common to several other reactions. When the rate of lactone formation in ethereal solution is studied, the results indicate that in complete absence of water the reaction does not occur. Very small quantities of water increase the velocity tremendously, however, so that in ethereal solutions containing only 1 per cent of water the velocity is three times that of an aqueous solution containing the same total concentration of acid; the conductivity of the ether-water solutions of hydrochloric acid is less than that of conductivity water. It is evident therefore that the velocity in ethereal solutions is not due to the undissociated molecule, nor can the catalytic activity be directly proportional to the acid concentration or to the hydrogen-ion concentration as determined by conductance. The authors conclude: "Since the catalytic activity is therefore not directly dependent on the solvent, the undissociated molecules of acid, the acid concentration, or the hydrogen-ion concentration, it is necessary to relate the observed activity to some other function of the acid catalyst. The experimental data seem to us to offer better qualitative evidence than has hitherto been offered that the reaction velocity is proportional to the hydrogen-ion activity as defined in the thermodynamic sense. From the activity concept, it is predictable that the velocity in ethereal solutions of hydrochloric acid saturated with water should be many times that of aqueous solutions of the same concentration of hydrogen chloride saturated with ether. For, hydrogen chloride distributes itself between ether-water mixtures in such a way that the chloride is mainly in the water layer, only slightly in the ethereal layer."

Ester Hydrolysis

There are very few reactions that have been more carefully studied than the hydrolysis of esters in aqueous acid solutions. We have at our disposal from among the multitude of experimental facts, data for all the possible range of conditions, namely, variation of the ester, variation of the acid, variation of temperature, variation of the concentration of ester, of acid and of water. The effect of the addition of both electrolytes and non-electrolytes has also been extensively studied. The result of all this study has been to give us a large number of conflicting hypotheses regarding the mechanism of the re-

action. The stoichiometric equation suggests a trimolecular reaction between ester, water and catalyst; in dilute aqueous solution the reaction should appear to be bimolecular since the water concentration is constant.

While the early work confirmed this, it soon became evident that the results obtained in stronger solutions and in presence of neutral salts could not be reconciled with the simple theory. Early attempts to overcome these difficulties by postulating direct ionization of the ester into $R'CO^+$ and OR^- or into $R'COO^-$ and R^+ [8] led to incorrect quantitative results. Stieglitz,[9] from a study of the hydrolysis of imido-esters, concluded that the reaction could best be explained by postulating double compound formation between the ester and catalyzing acid, the action being represented by the following equations:

$$C_6H_5C(:NH)OCH_3 + HCl \rightleftarrows [C_6H_5C(:NH)OCH_3,HCl]$$
$$[C_6H_5C(:NH)OCH_3,HCl] \rightleftarrows [C_6H_5C(:NH)OCH_3,H]^+ + Cl^-$$
$$[C_6H_5C(:NH)OCH_3,H]^+ + H_2O = C_6H_5COOCH_3 + NH_4^+$$

The positive ion of the salt is therefore the reacting substance and the acid catalyzes by forming larger amounts of the active ion, since the salt would ionize more extensively than the weak base. A similar assumption is made for ordinary ester hydrolysis, namely, that the complex oxonium ion, formed by combination with the hydrogen ion of the catalyzer, is the chief reacting component of the ester which is saponified by the water.

Complex Formation in Ester Hydrolysis

In order to give adequate consideration to this problem it is necessary to make a comprehensive survey of the possible compounds present in an acid aqueous solution of an ester. The formation of additive compounds in such solutions certainly disturbs the stoichiometric ratios very materially, and inasmuch as it appears most probable that the hydrolysis is effected in steps, with these compounds as intermediate products, it is clearly important to examine their character and stability as thoroughly as possible. It is undoubtedly the case that compounds of the type R.COOR',HX exist in mixtures of ester and acid. We have now to consider the stability of these complexes, the evidence with regard to their dissociation in aqueous solution, and the formation of addi-

[8] Zengelis, *Ber.*, 34, 198 (1901); Euler, *Z. physik. Chem.*, 36, 640 (1901).
[9] Stieglitz, *Am. Chem. J.*, 39, 29, 402 (1908); *idem, J. Am. Chem. Soc.*, 35, 1774 (1913).

tive compounds of other types in the presence of the third component, water.[10]

The progressive dissociation of ester-acid compounds on addition of water may be postulated as due to three distinct causes. In the first place, the effect may be purely diluent, the equilibrium point of the reaction $R.COOR',HX \rightleftarrows R.COOR' + HX$ being shifted to the right merely by the diminution in the concentrations of ester and acid as we proceed from the anhydrous system to a dilute aqueous solution. In the second place the water may disturb the equilibrium still further by combining with the free acid or ester to form binary complexes of the type HX,H_2O or $R.COOR',H_2O$. In the third place the water may combine with the ester-acid compound to give a ternary complex of the type $R.COOR',HX,H_2O$.

The first point may easily be investigated by preparing the ethyl acetate-trichloroacetic acid complex and measuring the freezing-point lowerings in benzene solution at various concentrations. These measurements when compared with the sum of the lowerings for the two components separately at the same concentrations are found to be much smaller, indicating that even in dilute benzene solution a large proportion of the compound is still existent. This is true, although in much less degree, of such systems as ethyl acetate-acetic acid in which even under the best conditions double compound formation is not extensive.

A most unexpected result was obtained on substituting water for benzene as solvent. The freezing-point depression curves for both water and benzene are practically identical although we should expect water to dissociate these compounds to a far greater degree than benzene. In such a system as ethyl acetate and benzene in which we have a polar solute and a non-polar solvent, the internal pressures of the two components in the liquid state is markedly different. An abnormally small depression of the freezing-point is a general characteristic of such systems [11] so that most probably very extensive dissociation of the ester-acid compound on addition of water does occur, but the negative deviation from Raoult's law is obscured by a simultaneous positive deviation from Raoult's law due to the internal pressure factor.

On this basis also we may conclude that ethyl acetate is fairly extensively hydrated in aqueous solution in spite of the fact that the freezing-point curve of the ester-water system is almost ideal; ethyl acetate

[10] See Kendall and Booge, *J. Chem. Soc.*, **127**, 1768 (1925); Kendall and King, *ibid.*, **127**, 1778 (1925).

[11] See Hildebrand, "Solubility," *Am. Chem. Soc.*, Monograph Series, **1924**.

is a "pseudo-ideal" solute in water, two opposing factors practically counterbalancing each other. Owing to the great difference of internal pressure of the two components the experimental depression should be considerably less than the ideal, and the only factor that could increase the depression back to normal is extensive compound formation between ester and water. Further support for this is to be found in the fact that heat is evolved when ethyl acetate dissolves in water, whereas partially miscible liquids usually absorb heat on mixing; also the rapid increase in the solubility of the ester as the temperature is

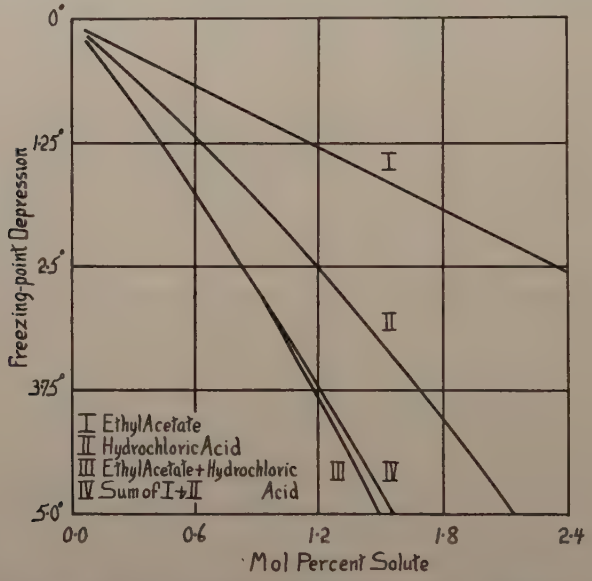


Fig. 9.—System: Ethyl Acetate—Hydrochloric Acid. Water as Solvent.

lowered suggests that a compound is formed, the stability of which increases as the temperature is lowered; finally, the considerable contraction that occurs on mixing ethyl acetate and water is most simply explained on the assumption of compound formation.

We may conclude with some confidence that addition compounds occur in all three binary systems, ester-acid, acid-water and ester-water. It now becomes necessary to determine to what extent these survive in the ternary system and whether any ternary compounds are formed. The results shown in Figure 9 demonstrate that ternary complexes cannot exist in any significant quantity in the solution; in fact the ester-acid complex $CH_3COOC_2H_5,HCl$ is also completely dissociated, for the

freezing-point depressions induced by acid and ester taken together (curve III) are almost identical with the sum of the depressions induced by corresponding concentrations of the two separately (curve IV). If the ester-acid complex $CH_3COOC_2H_5,HCl$ were completely stable in solution, we should expect its curve to follow approximately the ethyl acetate (or ideal) curve (I) in the event of it being a non-electrolyte, or the hydrochloric acid curve (II) in the more probable event of its being a strong electrolyte giving the ions $CH_3COOC_2H_5,H^+$ and Cl^-. An intermediate position, between (I) and (II) or between (II) and (IV),

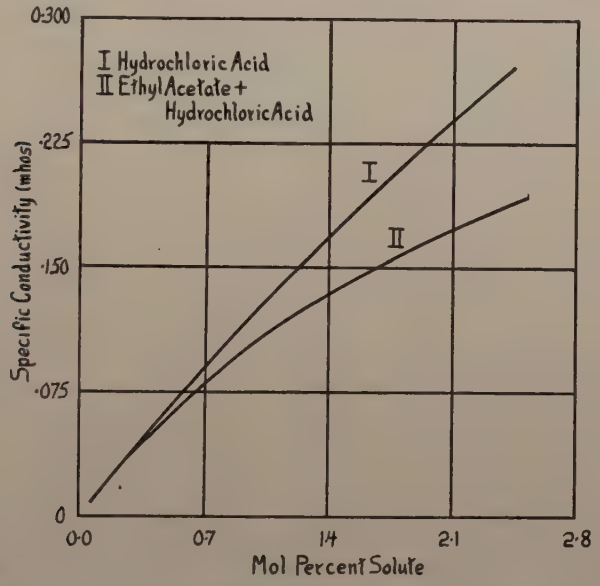


FIG. 10.—System: Ethyl Acetate—Hydrochloric Acid. Water at 0° as Solvent.

would follow from partial dissociation. The actual position of the curve, however, indicates complete dissociation of the compound into its components, a result which we might expect by considering the ester and water as rival bases, competing for the possession of the hydrochloric acid. Alone, each is able to furnish a stable additive compound (or oxonium salt), but in dilute aqueous solution the enormous excess of water and its more highly basic character lead to essentially complete destruction of the ester-acid complex. In general we may conclude from measurements of freezing-point depression that ternary complexes and ester-acid additive compounds do not exist in any sig-

nificant quantity in aqueous solutions, but that ester-water additive compounds may exist to considerable extent.

We may now consider these conclusions in the light of measurements of the conductivity of these solutions and also reaction rate measurements. In Figure 10 is shown the conductivity curve for hydrochloric acid—water and a system consisting of equimolar parts of hydrochloric acid and ethyl acetate in water. The addition of an equivalent quantity of ethyl acetate reduces the specific conductivity considerably, the effect being more pronounced the higher the concentration. The first and most obvious means of accounting for the observed decrease is to assume compound formation of ester with acid in the solution; whether the complex R.COOR′,HX ionizes into $[R.COOR',H]^+$ and X^- or does not ionize, the conductivity would be diminished. The second explanation is that the addition of ester causes a decrease in the dielectric constant of the solution and so reduces the extent of ionization of the acid. The third possible explanation is that the addition of ester simply decreases the mobility of the ions without changing their nature.[12]

The first explanation may be ruled out because it is in direct conflict with the freezing-point measurements which indicate that there is no survival of any ester-acid complex in the aqueous system. A number of reasons may be deduced for ruling out the second hypothesis: it is in conflict with the freezing-point data and also it is necessary to assume an enormous decrease in the dielectric constant for the addition of a small amount of ester; the addition of ester decreases the specific conductivity of a neutral salt just as effectively as it does that of an acid solution and there can hardly be extensive compound formation between an ester and a neutral salt in aqueous solution; finally, the addition of ethyl acetate is without effect on the rate of sucrose inversion in an acid solution.[13] We may conclude therefore that there is no significant change in the hydrogen-ion concentration on addition of ethyl acetate, its effect merely being to reduce the ionic mobilities of the ions.

Kendall and King confirmed the results of other workers that the rate of hydrolysis of ethyl acetate by hydrochloric acid increases much more rapidly than the specific conductivity and more rapidly even than the molecular concentration of the acid. They conclude: "This may

[12] Compare alcohol-water mixtures, Godlewski, *Z. physik. Chem.*, **51**, 751 (1905).

[13] See also Henri and des Bancels, *C. R. Soc. Biol.*, **53**, 784 (1901); Griffith and Lewis, *J. Chem. Soc.*, **109**, 67 (1916).

be interpreted in two ways. First of all, it may be regarded as indicative of the fact, already noted in the freezing-point depression curve, that the 'activity' of the hydrogen ion increases more rapidly than the acid concentration, even when this is expressed in molecular units. Alternately, it may be construed, according to the theory that the non-solvated hydrogen ion alone is catalytically active (recently revived by Rice, *J. Am. Chem. Soc.*, 45, 2808 (1923)), as signifying that the non-hydrated fraction of the hydrogen ion increases steadily as the concentration of the two solutes is increased, owing to the diminishing concentration of free water present in the solution. The two statements are not however mutually exclusive, in all probability, but merely different methods of expressing the same situation."

This increase in the value of the velocity constant with increase in the concentration of ester was first discussed by Ostwald [14] who attributed the increase to the fact that in the stronger solutions appreciable amounts of ester remain unchanged at the equilibrium point. This would give a wrong value for the initial concentration of ester which is obtained by subtracting the final titer of the solution from the initial titer, assuming complete hydrolysis. Griffith and Lewis,[15] however, in a very careful study of the reaction show that this is quite inadequate to account for the observed variation. In the first place the simple velocity equation is obviously incorrect because the reaction is bimolecular and reversible; the velocity equation would be therefore,

$$\frac{dx}{dt} = k_1 (a - x)(b - x) - k_2 x^2$$

where a and b are the initial concentrations of ester and water respectively and x is the number of moles of ester reacting in t minutes. The equilibrium constant of the reaction may be written,

$$\frac{[\text{ester}] \times [\text{water}]}{[\text{alcohol}] \times [\text{acetic acid}]} = K = \frac{k_2}{k_1}$$

so that we have

$$\frac{dx}{dt} = k_1[(a - x)(b - x) - Kx^2].$$

The equilibrium constant of the reaction was measured in the presence of 0.1 *N*, 0.2 *N*, and 1 *N* hydrochloric acid, a mean value of 4.6 being obtained.

[14] Ostwald, *J. pr. Chem.*, **28**, 449 (1883).
[15] Griffith and Lewis, **J. Chem. Soc., 109,** 67 (1916).

Griffith and Lewis found that the values of k_1 calculated from the more complete velocity equation still increased with increasing concentration of ester. It may be noted here, that for concentrations of ester less than 0.2 *M*, the back reaction and the water concentration may be neglected without appreciable error. The authors finally conclude that this deviation may be ascribed to complex formation of the type

$$\text{ester} + \text{water} \rightleftarrows \text{ester-water}$$

If a and b are the initial concentrations of ester and water respectively and e is the equilibrium concentration of the complex, the equilibrium constant will be,

$$K = \frac{e}{(a-e)(b-e)}.$$

Since in the experiments a is small compared to b, e will be still smaller and we can write,

$$K = \frac{e}{b(a-e)}, \text{ or } e = \frac{K\,a\,b}{1 + K\,b}$$

If the ester-water complex is really the reacting substance we may substitute e instead of a in the velocity equation. Now as the concentration of ester, a, increases, the concentration of the complex, e, also increases but at a more rapid rate because the complex should be least dissociated in the 1:1 mixture. Griffith and Lewis conclude, however, that the increase calculated on the basis of mass action alone is not sufficient and they postulate an additional factor, namely, that when the water content is diminished, the medium becomes richer in methyl acetate, and therefore, as a whole, must act as a feebler dissociating agent on the additive complex, ester-water, which is therefore produced in greater quantity than would be the case if the physical action of the solvent remained constant.

We may conclude on the basis of the evidence available that the mechanism of hydrolytic reactions is represented by two stages, the first of which consists of a rapid formation of a substrate—water complex which slowly reacts with a catalyst to give the products of the hydrolysis.

Esters of Strong Acids

There are relatively few exceptions to the rule that strong acids accelerate the rate of saponification of esters; exceptions are the esters

of phosphoric acid,[16] the esters of sulfonic acids,[17] di-substituted esters of sulfuric acid,[18] lactones [19] and benzyl chloride.[20] Hydrogen ion has no effect on the hydrolysis of these compounds.

Recently Olivier and Berger,[21] from a study of the esters derived from strong acids, concluded that these are not hydrolyzed by hydrogen ion. The rate of saponification of benzyl chloride in presence of sulfuric acid is proportional to the concentration of the benzyl chloride but is independent of the acid concentration. Similar results are obtained by hydrolyzing monochlorohydrin [22] in aqueous solution both with and without sulfuric acid. Hydrogen ion has no effect on the rate of hydrolysis of *n*-butyl chloride, isobutyl chloride or ethyl nitrate. This behavior therefore appears to be common to the esters of all strong mineral acids; the same effect occurs also with the esters of strong organic acids, for the hydrolysis of methyl trichloroacetate is only slightly accelerated by hydrochloric acid. The reaction

$$CH_2ClCOOH + H_2O = CH_2OHCOOH + HCl$$

is not affected [23] by a strong acid.

Another curious anomaly occurring with these esters is that they are fairly easily hydrolyzed by water alone. This fact, together with the fact that these esters are readily hydrolyzed by alkali, suggests that only hydroxyl ion is effective in promoting the hydrolysis; in neutral and acid solution the glass surface may be the active agent. These curious results find a counterpart in the esterification process,[24] since in presence of hydrochloric acid, weak organic acids, and when there is no added catalyst, the stronger acids esterify more quickly than weaker acids.

Substitution and Rate of Hydrolysis

The effect of substitution on the rate of hydrolysis of fatty acid esters has been studied with some degree of completeness. This is possible because a number of groups can be substituted in the α and β

[16] Cavalier, *Ann. chim. phys.*, **18**, 449 (1899); Wegscheider, *Ber.*, **52**, 235 (1919).
[17] Wegscheider, *Z. physik. Chem.*, **41**, 52 (1902); Wegscheider and Furcht, *Monatsh.*, **23**, 1093 (1902); Practorius, *ibid.*, **26**, 1 (1905).
[18] Kreman, *Monatsh.*, (a) **28**, 13 (1907); (b) **38**, 53 (1917); Klemenc, *ibid.*, **38**, 553 (1917).
[19] Johansson and Sebelius, *Ber.*, **51**, 480 (1918).
[20] Olivier, *Rec. trav. chim.*, **41**, 303 (1922).
[21] Olivier and Berger, *Rec. trav. chim.*, **41**, 637 (1922).
[22] See also Senter, *Proc. Chem. Soc.*, **24**, 89 (1908).
[23] Senter, *J. Chem. Soc.*, **91**, 460 (1907).
[24] Sirks, *Rec. trav. chim.*, **27**, 248 (1908).

positions without being appreciably affected by the hydrolysis of the ester. For example in the hydrolysis of chloro- and bromoacetic esters there is no appreciable hydrolysis of the chlorine or bromine atom even after several weeks at the temperatures used. Some of the results obtained[25] are shown in Table XIII; the temperature coefficient of the unsubstituted esters is approximately 2.4 but is slightly lower (approximately 2) for the α substituted esters. The effect of the position of the halogen atom was studied by hydrolysis of esters of chloro- and

TABLE XIII

VELOCITY CONSTANTS ($k \times 10^4$) CALCULATED FOR A SOLUTION OF 1 *M* ESTER AND 1 *N* HYDROCHLORIC ACID AT 25°

	Methyl	Ethyl	Propyl	Isobutyl
Acetates	66.0	59.6		66.3
Chloroacetates	43.8	41.4	41.4	42.8
Bromoacetates	50.8	47.6	52.6	49.4

bromopropionic acid. The rates of hydrolysis of the ethyl esters of propionic acid, α-chloropropionic acid and α-bromopropionic acid are in the ratio 100:40:30; for propionic acid, β-chloropropionic acid and β-bromopropionic acid the ratios are 100 : 14 : 11, so that substitution in the β position causes the greater diminution in the velocity of hydrolysis. The temperature coefficient k_{35}/k_{25} for ethyl propionate and the β-substituted esters is 2.5 but for the α-substituted esters is 2. The presence of the cyanide group diminishes the velocity considerably,[26] as may be seen from the following relative rates: ethyl acetate 100, ethyl chloroacetate 67 and ethyl cyanoacetate 15; the temperature coefficient k_{35}/k_{25} for ethyl cyanoacetate is 2.3. Substitution of hydroxy or alkyloxy groups produce similar results, which are shown in Table XIV. The temperature coefficient k_{35}/k_{25} for all these reactions is approximately 2.4.

We may conclude therefore that substitution of α- or β-hydrogen atoms reduces the rate of hydrolysis of fatty acid esters, the reduction being greater when one of the β-hydrogen atoms is substituted. This applies only to the acid hydrolysis of esters, very different results being obtained when these esters are hydrolyzed in an alkaline medium.

The velocity of saponification of ethyl acetate in alkaline solution seems to have been measured first by Warder.[27] Soon after came a

[25] Drushel and Hill, *Am. J. Sci.*, **30**, 72 (1910); Drushel, *ibid.*, **34**, 69 (1912).
[26] Drushel, *Am. J. Sci.*, **33**, 27 (1912).
[27] Warder, *Ber.*, **14**, 1361 (1881).

TABLE XIV

HYDROLYSIS CONSTANTS OF HYDROXY AND ALKYLOXY ESTERS IN ACID SOLUTION AT 25°

Ester		k
Ethyl Acetate	CH_3COOEt	100
Ethyl Glycollate	$CH_2(OH)COOEt$	106
Ethyl Methyloxyacetate	$CH_2(OCH_3)COOEt$	59
Ethyl Ethyloxyacetate	$CH_2(OC_2H_5)COOEt$	56
Ethyl Propionate	CH_3CH_2COOEt	110
Ethyl Lactate	$CH_3CH(OH)COOEt$	113
Ethyl Glycerate	$CH_2(OH)CH(OH)COOEt$	28.6
Ethyl α-Ethyloxypropionate	$CH_3CH(OC_2H_5)COOEt$	30.5
Ethyl β-Ethyloxypropionate	$CH_2(OC_2H_5)CH_2COOEt$	22
Ethyl Butyrate	$CH_3CH_2CH_2COOEt$	80
Ethyl Isobutyrate	$(CH_3)_2CHCOOEt$	62
Ethyl α-Hydroxyisobutyrate	$(CH_3)_2C(OH)COOEt$	62

series of very accurate and comprehensive measurements by Reicher,[28] who determined the relative effects of various bases and also showed that the effect of the alcohol radical in the ester is practically constant. Methyl esters decompose most rapidly and the velocity decreases up the series; the differences, however, are exceedingly slight beyond about the first three members. Reicher's experiments with the esters of different acids pointed toward a decrease in velocity with increasing molecular weight. Substitution of α- and β-hydrogen atoms causes an increase [29] in the rate of saponification, often a very great increase

[28] Reicher, *Ann.*, **228**, 257 (1885).

[29] Dean, *Am. J. Sci.*, **35**, 605 (1913); Findlay and Turner, *J. Chem. Soc.*, **87**, 747 (1905); Findlay and Hickmans, *ibid.*, **95**, 1004 (1909).

(Table XV); there are some irregularities, however. The temperature coefficients for alkaline hydrolysis are approximately the same; k_{25}/k_0 is about 5.3 which gives $Q = 10{,}800$ and $k_{35}/k_{25} = 1.8$. In acid solution both the substituted and unsubstituted isobutyrates decompose more slowly than the corresponding normal esters. The opposite is true for alkaline solution.

TABLE XV

SAPONIFICATION OF SUBSTITUTED FATTY ACID ESTERS BY AQUEOUS SODIUM HYDROXIDE AT 25°

Ester		k
Ethyl Acetate	CH_3COOEt	100
Ethyl Glycollate	$CH_2(OH)COOEt$	1000
Ethyl Methyloxyacetate	$CH_2(OCH_3)COOEt$	1950
Ethyl Ethyloxyacetate	$CH_2(OC_2H_5)COOEt$	990
Ethyl Propionate	CH_3CH_2COOEt	90
Ethyl Lactate	$CH_3CH(OH)COOEt$	997
Ethyl Hydracrylate	$CH_2(OH)CH_2COOEt$	154
Ethyl Glycerate	$CH_2(OH)CH(OH)COOEt$	870
Ethyl Butyrate*	$CH_3CH_2CH_2COOEt$	302
Ethyl α-Hydroxybutyrate*	$CH_3CH_2CH(OH)COOEt$	2650
Ethyl Isobutyrate*	$(CH_3)_2CHCOOEt$	203
Ethyl α-Hydroxyisobutyrate*	$(CH_3)_2C(OH)COOEt$	709
Ethyl β-Hydroxybutyrate*	$CH_3CH(OH)CH_2COOEt$	925

* These experiments were performed at 0°; the results given in the table were obtained by multiplying the figures obtained at 0° by 5.3 which is the average value of k_{25}/k_0.

We may conclude therefore that in acid hydrolysis the esters of stronger acids are hydrolyzed more slowly than the esters of weaker acids, but in alkaline solution the esters of stronger acids are more easily hydrolyzed. There are exceptions to this rule such as the greater diminution of velocity in acid solution caused by β-substitution than α-substitution. The character of the bonds in the -C-O-R group in the ester gives a clue to this behavior. Consider an acid,

$$R-\overset{\overset{(1)}{|}}{\underset{\underset{O}{\|}}{C}}-\overset{\overset{(2)}{|}}{O}-H\ ;$$

if the acid is very weak, bond (2) will be strong and bond (1) will be weak, whereas the opposite will be true when R is a negative group and the acid strong. We may postulate also that this same relationship between bond (1) and bond (2) holds in the ester of a given acid. Suppose we postulate further that in hydrogen-ion catalysis bond (1) is broken whereas in hydroxyl-ion catalysis bond (2) is broken; with some exceptions this provides a reasonable explanation of the results obtained in ester catalysis. Some work of Reid [30] supports the conclusion that bond (1) is the weaker in the acid catalysis of esters of weak acids. If we esterify an acid using a mercaptan instead of an alcohol we can distinguish between the OH group of the acid and the SH group of the alcohol. Using benzoic acid we find that water is eliminated and the system reaches a well defined equilibrium state exactly analogous to an acid and an alcohol:

$$C_6H_5CO\,\boxed{OH+H}\,SR \rightleftarrows C_6H_5CO\,\boxed{SR+H}\,OH.$$

This result in conjunction with the esterification of thioacids,

$$C_6H_5CO\,\boxed{SH+H}\,OC_2H_5 = C_6H_5COOC_2H_5 + HSH,$$

suggests that bond (1) is broken in the acid hydrolysis of the esters of weak acids. This hypothesis leads to an interesting prediction: a strong acid when esterified by a mercaptan should yield hydrogen sulfide instead of water because in this case bond (2) is the weaker.

Hydrolysis of Amides

The hydrolysis of amides may be assumed to have a mechanism similar to reactions in which an ester is hydrolyzed; the amide first

[30] Reid, *Am. Chem. J.*, **43**, 489 (1910); Pratt and Reid, *J. Am. Chem. Soc.*, **37**, 1934 (1915); Sachs and Reid, *ibid.*, **38**, 2746 (1916).

forms a complex compound with the water which then hydrolyzes on collision with either a hydrogen ion or a hydroxyl ion. Since amides are in general more basic than esters we may assume complex formation with the water to be more extensive than with esters. The study of the hydrolysis of amides is nothing like so extensive as that of esters, partly, doubtless, because amides are not so easily hydrolyzed, since they require temperatures of 40°-100° to give measurable rates; in addition the liberation of ammonia in the alkaline hydrolysis makes it somewhat difficult to determine the catalyst concentration during the course of the reaction.

Reid [31] has made several studies of the hydrolysis of acid amides. Homologs of benzamide were hydrolyzed at 100° and it was found that substitution in the ring diminishes the rate of hydrolysis by hydrogen ions, *ortho* substitution having the greatest effect. *Ortho* substitution diminishes the rate to about one tenth of that of benzamide, and the reduction is apparently not related to the acid or basic character of the substituent group. It is surprising to note the small effect of *meta* and *para* substitution, the change in velocity rarely exceeding 25 per cent. The effect of substitution on the rate of hydrolysis in alkaline solution is somewhat erratic; here *ortho* substitution usually reduces the velocity but *para* or *meta* substitution may increase or decrease the velocity.

It would seem more hopeful to study the substituted fatty acid amides with the expectation of finding results parallel to those of the substituted fatty acid esters. This does not appear to be the case because Sulo Kilpi [32] found that in the acid hydrolysis of alkyloxy amides, substitution in the α- or γ-position accelerates, but in the β-position retards the hydrolysis of amides. Several other studies [33] of the hydrolysis of amides have been made; however they are not in very good agreement with each other. Different authors have obtained values of the temperature coefficient in acid solution varying from 2.5 to 3.3.

Hydrolysis of Sucrose

Sucrose has been the most studied of any organic compound from the point of view of reaction kinetics. A résumé of the work up to

[31] Reid, *Am. Chem. J.*, **21**, 284 (1899); *idem, ibid.*, **24**, 397 (1900); see also Acree and Nirdlinger, *ibid.*, **38**, 489 (1907).
[32] Sulo Kilpi, *Z. physik. Chem.*, **80**, 165 (1912).
[33] Euler and Rudberg, *Z. anorg. Chem.*, **127**, 244 (1923); Crocker, *J. Chem. Soc.*, **91**, 593 (1907); Crocker and Lowe, *ibid.*, **91**, 955 (1907); Preskoff and Meyer, *Z. physik. Chem.*, **82**, 129 (1913).

1906 is given by Caldwell [34] who states that up to that time 140 papers were published on the hydrolysis of cane sugar. A steady flow of papers has since been appearing so that now several hundred kinetic studies of this reaction have been made. Two main points are under discussion, first, whether the additive law holds for the partly hydrolyzed sucrose solutions, and second, what is the mechanism of the reaction. For the preliminary discussion of the reaction we will assume a mechanism similar to the one adopted for ester hydrolysis;

$$\text{sucrose} + H_2O \rightleftarrows \text{sucrose},H_2O \qquad (1)$$

$$\text{sucrose},H_2O + H^+ = \text{glucose} + \text{fructose} + H^+. \qquad (2)$$

Reaction (1) is fast and the hydrate is supposed to be present in small concentration; reaction (2) is the slow measured reaction. The measured rate therefore should be proportional to the concentration of sucrose and the concentration of hydrogen ion; on this assumption and on the assumption that the change in concentration of the sucrose is proportional to the change in optical rotation the constants obtained do not vary [35] more than 1 or 2 per cent during the course of an experiment. The temperature coefficient of sugar hydrolysis is much higher than that of ester hydrolysis having the value $k_{35}/k_{25} = 4.1$.

We may now consider the relation between the rate of the reaction and the polarimetric readings. In order to obtain a velocity constant we must know the concentration of acid catalyst which remains constant throughout the reaction, the initial concentration of cane sugar a and the concentration of cane sugar $(a - x)$ after t minutes; the ratio $a/(a - x)$ is put equal to $(\lambda_o - \lambda_\infty)/(\lambda_t - \lambda_\infty)$ where λ represents the polarimeter reading. The difficulty of obtaining a reliable value for λ_o, the angle of rotation at the beginning of the reaction, was pointed out [36] and it was shown that this difficulty could be avoided by plotting values of log $(\lambda_t - \lambda_\infty)$ against t, and extrapolating to $t = 0$.

The second point which we must consider is the assumption that the amount of sugar hydrolyzed is a linear function of the change in rotation. Hudson [37] has pointed out that strict proportionality between change in rotation and amount hydrolyzed is possible only if the specific rotations of sucrose, glucose and fructose do not change with concentration, a condition that is only approximately fulfilled in the case of the pure sugars. For sucrose and glucose the variation is negligible but

[34] Caldwell, *Brit. Assoc. Adv. Sci. Rep.*, 351 (1906).
[35] Lamble and Lewis, *J. Chem. Soc.*, **107**, 233 (1915).
[36] Rosanoff, Clarke and Sibley, *J. Am. Chem. Soc.*, **33**, 1911 (1911).
[37] Hudson, *J. Am. Chem. Soc.*, **32**, 885 (1910).

in the case of fructose it is appreciable in magnitude and the variation is in such a direction as to cause an apparent increase in the velocity coefficients. Nelson and Beegle [38] have found that the specific rotation of fructose is affected by the presence of sucrose and the effect is in such a direction as to compensate the variation in specific rotation with concentration in the case of the hydrolysis of sucrose. Vosburgh [39] from a careful study of these factors concludes that the velocity constants are too high by about 0.4 per cent when sodium light is used and appreciably less so if the 5461 λ line from a mercury vapor light is used in the polariscopic measurements.

A more serious error may arise from successive reactions of the products of the hydrolysis of sucrose. The reaction is actually an exceedingly complex change in which the monosaccharides are subject to structural and steriochemical rearrangements. The reaction may be represented by some such scheme as the following: [40]

$$\begin{array}{ccccc} & \overset{k_1}{} & & \overset{k_4}{} & \\ \text{Sucrose} & \longrightarrow & \alpha\text{-glucose} + \alpha\text{-fructose} & \rightleftarrows & \alpha\text{-fructose} \\ & & \uparrow\downarrow k_2 & \uparrow\downarrow k_3 & \uparrow\downarrow k_5 \\ & & \beta\text{-glucose} & \beta\text{-fructose} & \beta\text{-fructose} \\ & & \text{(butylene-oxidic)} & \text{(amylene-oxidic)} & \text{(butylene-(oxidic)} \end{array}$$

All these substances are optically active so that strict proportionality between the concentration of sucrose and $\lambda_t - \lambda_\infty$ can only be possible when k_1 is relatively small compared with the mutarotation coefficients. When invertase is used as catalyst, k_1 is generally large while k_2 and k_5 have practically their minimum values,[41] so that we can no longer expect any simple proportionality between the concentration of sucrose and the polarimetric readings. In the presence of acids, however, k_1 is relatively small compared with the mutarotation constants, so that the ordinary formula gives approximately constant values for k_1.

Pennycuick [42] has shown that for accurate work the mutarotational lag is not negligible. For example if an acid solution of cane sugar is neutralized by alkali and a reading taken immediately, a new value will be obtained after some minutes owing to the gradual attainment

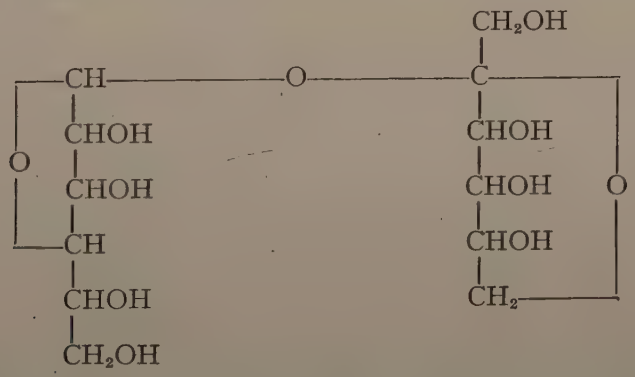
[38] Nelson and Beegle, *ibid.*, **41**, 572 (1919).
[39] Vosburgh, *ibid.*, **43**, 219 (1921).
[40] Haworth and Law, *J. Chem. Soc.*, **109**, 1314 (1916); Haworth and Linnell, *ibid.*, **123**, 294 (1923).
[41] O'Sullivan and Thomson, *J. Chem. Soc.*, **57**, 834 (1890); Hudson, *J. Am. Chem. Soc.*, **30**, 1564 (1908); Nelson and Beegle, *ibid.*, **41**, 559 (1919).
[42] Pennycuick, *J. Chem. Soc.*, **125**, 2049 (1924); *idem*, *J. Am. Chem. Soc.*, **48**, 6 (1926).

of the mutarotational equilibrium. It is obvious that if the mutarotational lag has an appreciable effect, this will be greatest during the earlier stages of the reaction when the monosaccharides are present at minimum concentrations, and the actual velocity of change consequently also at minimum value. As the hydrolysis progresses, the actual velocity of inversion of the cane sugar diminishes whereas the velocities of the mutarotational changes increase. Pennycuick shows that the lag passes through a maximum at a comparatively early stage in the action, when less than 10 per cent of the sucrose has been inverted. He gives a very full treatment of the reaction both from the theoretical and experimental side and points out that the existence of the lag will not interfere with the applicability of the short interval formula,

$$k_1 = \frac{1}{t_2 - t_1} ln \frac{\lambda_{t_1} - \lambda_\infty}{\lambda_{t_2} - \lambda_\infty},$$

provided that it is not applied very early in the action. This is so because after a brief time interval the lag becomes strictly proportional to the concentration of the remaining sucrose, with the result that the graph of log $(\lambda_t - \lambda_\infty)$ with lag and that of log $(\lambda_t - \lambda_\infty)$ without lag, against t, become strictly parallel, and both have the slope k_1, the inversion constant.

The actual mechanism of the inversion of sucrose is still far from settled. Following Haworth and Linnell [43] we may write the constitutional formula for sucrose as,



Such a molecule will almost certainly be heavily hydrated in aqueous solution.[44] For the consideration of the mechanism of the hydrolysis

[43] Haworth and Linnell, *J. Chem. Soc.*, **123**, 296 (1923).

[44] For a complete discussion of the hydration of sucrose see Scatchard, *J. Am. Chem. Soc.*, **43**, 2406 (1921).

however we are not directly concerned with the hydration of the various hydroxyl groups but only with the hydration of the acetal oxygen joining the glucose and fructose residues. Following the scheme adopted for ester hydrolysis we may write the preliminary change in sucrose inversion as,

$$\text{(hydrated sucrose)} + H_2O \rightleftarrows \text{(hydrated sucrose)},H_2O,$$

which represents the equilibrium between the water and the oxygen atom joining the two portions of the sucrose molecule. This equilibrium is supposed to be established practically instantaneously and the concentration of the compound (hydrated sucrose),H_2O is supposed to be small. The second reaction is the slow measured change which may be represented as follows:

$$\text{(hydrated sucrose)},H_2O + H^+ = \text{hydrated glucose} + \text{hydrated fructose} + H^+.$$

As in ester hydrolysis this scheme explains in a semiquantitative way the general facts of the inversion process. It does not seem likely that further advance will be made along these lines until we have further knowledge regarding the extent of formation of double compounds in solution. It will be noted that the compound (hydrated sucrose), H_2O is a residual molecule and should therefore change in concentration with temperature depending on its heat of formation. The temperature coefficient k_{35}/k_{25} of sucrose inversion is approximately 4 which is much higher than the value for a non-hydrolytic reaction; we must therefore postulate that the compound (hydrated sucrose),H_2O increases in concentration with rise in temperature, i.e., it is an endothermic compound. While this is an exception to the general rule that addition compounds are exothermic it must be remembered that this compound is not a simple 1 : 1 compound. The water molecule we are considering is probably the least strongly combined of all the water molecules, being in the middle of the chain and attached to an oxygen atom. It is quite possible that the combination of this last molecule of water is accompanied by absorption of heat, since the free energy evolution must be small.

Several extensive studies of the mechanism of this reaction have been made from the thermodynamic point of view. Jones and Lewis [45] measured the activity of the hydrogen ion by means of the hydrogen electrode. Assuming that the speed of reaction is proportional to this

[45] Jones and Lewis, *J. Chem. Soc.*, **117**, 1120 (1920); see also Fales and Morrell, *ibid.*, **44**, 2071 (1921).

activity of the hydrogen ion rather than to its concentration they find it also proportional to the concentration of water in moles per liter, and they draw the conclusion that the reaction proceeds by the combination of a molecule of sugar with a hydrogen ion, and that this complex ion reacts with one molecule of water to form glucose and fructose and to re-form the hydrogen ion. Scatchard,[46] in a review of this work, extended the substitution of activity for concentration to the other reactants as well as to the hydrogen ion, but his conclusions as to the mechanism of the reaction are very different from those of Jones and Lewis. He concludes that the inversion of sucrose is a reaction of the sixth order with respect to the water, the results being interpreted as indicating the existence of a hexahydrate of sucrose.

Moran and Lewis confirmed Scatchard's conclusions in so far as it is necessary to determine the activities of all the reactants, but disagreed as to the mechanism. They postulate a slow reaction between a sucrose dihydrate and an unhydrated hydrogen ion to form a complex which decomposes at a rapid rate. They also find it necessary to take into account the viscosity of the solution, considering that the frequency of collision is a function of the viscosity and through influencing this frequency the viscosity affects reaction speed; hence viscosity should have no effect on a unimolecular reaction. In the case of the reaction of sucrose with hydrogen ion the heavier sucrose molecule moves so much more slowly that it may be considered as motionless, and the effect of viscosity on the reaction speed is proportional to its effect on the mobility of hydrogen ion as measured by conductivity; it is inversely proportional to the square root of the viscosity. It is difficult however to decide finally whether viscosity has really any appreciable influence on reaction rate and the matter can yet only be regarded as undecided. A good discussion of this is given in a recent paper.[47]

Esterification

We may conclude this chapter by a discussion of the reverse reaction to hydrolysis, namely, esterification. In spite of the immense amount of work done on these reactions it is not yet possible to formulate the results in a satisfactory quantitative manner. If we consider a dilute solution of acetic acid in ethyl alcohol (no water being present) and we pass in dry hydrogen chloride, the normal behavior would be

[46] Scratchard, *ibid.*, **43**, 2387 (1921).
[47] *Idem, ibid.*, **45**, 1583 (1923).

for the rate to be proportional to the concentration of acetic acid. Actually we find that as the acetic acid reacts the rate of the reaction falls very much more rapidly. We might find for example that when half the acetic acid is esterified, the rate, instead of being one half of the initial rate, is only one tenth to one hundredth of the initial rate. This is due to the extremely high negative catalytic action of small quantities of water, the mechanism of which is not yet understood. Linked up closely with this is the mechanism of the catalytic action and the relative rôles played by the undissociated acid, hydrated hydrogen ion, alcoholated hydrogen ion, dry hydrogen ion and possible compounds between the substrate and hydrogen ion. The situation is rendered still more mystifying by the recent observation of Taylor and Close [48] that the rate of lactone formation in dry ether is extremely small but in dry alcohol is extremely large. From this and other recent work it is probable that we may neglect the catalytic activity of the undissociated molecule, but we are by no means certain which of the other hypotheses is correct or even whether some new explanation may finally be shown to agree with the observations. Undoubtedly much of the difficulty of interpreting the results is due to the fact that most of the reactions studied in anhydrous media produce water as one of the resultants and owing to this, the character of the medium changes at a very rapid rate. This difficulty has been avoided by Reid [49] who studied the alcoholysis of acid amides; with benzamide and ethyl alcohol in acid solution we have,

$$C_6H_5CONH_2 + HOC_2H_5 + HCl = C_6H_5COOC_2H_5 + NH_4Cl.$$

This is a clean reaction and can be investigated both in absolute alcohol solution and in alcohol solutions containing small amounts of water. Reid found that the reaction rate is proportional to the concentration of benzamide and to the concentration of acid, and, as with other reactions, is greatly sensitive to the presence of small quantities of water which show the usual retarding effect.

Goldschmidt [50] in an endeavor to explain this type of reaction assumes that the reactive substance is an additive compound of the hydrogen ion and alcohol, $[C_2H_5OH,H]^+$. This is supposed to have very high catalytic power compared to the hydrated hydrogen ion, $[H_2O,H]^+$; when water is added the hydrogen ion is supposed to go largely to the

[48] Taylor and Close, *J. Phys. Chem.*, **29**, 1085 (1925).
[49] Reid, *Am. Chem. J.*, **41**, 483 (1909).
[50] Goldschmidt, *Z. Elek. Chem.*, **15**, 4 (1909).

water so that small additions of water should give a great diminution of catalytic activity. Lapworth [51] assumes that only the unsolvated hydrogen ions are catalytically active and that they are much more plentiful in alcohol than in water of the same concentration of total acid; the addition of small quantities of water to the alcohol results in the formation of inactive $[H_2O,H]^+$. Bredig, Stieglitz, Acree and others have adduced much evidence in favor of the view that it is the complex cation formed from the amide, acid, ester, lactone, etc., by the addition of the hydrogen ion which is the reactive compound. Reid (*loc. cit.*) assumes that the solvated hydrogen ion may add to the substrate and in this way adduces an explanation of the phenomena. Until we know more about the mechanism of catalysis it is not possible to decide between these various hypotheses.

[51] Lapworth, *J. Chem. Soc.*, **93**, 2187 (1908), see also Rice, *J. Am. Chem. Soc.*, **45**, 2808 (1923).

Chapter VII.

Aliphatic Hydrocarbons.

The lack of chemical reactivity of saturated paraffin hydrocarbons is reflected in the practically complete absence of any complex compound formation. It may be, however, that there is some tendency for such complexes to be formed and as evidence may be cited the use of aluminium chloride as catalyst for cracking paraffin hydrocarbons,[1] an application which suggests that the aluminium chloride may exert a similar though much feebler action to that exerted in the aromatic series. Also the measurable affinity of paraffin hydrocarbons for water [2] and their appreciable solubility in it [3] indicate an appreciable degree of unsaturation.

Owing to their great stability, the study of the paraffins on oxidation, halogenation, sulfonation or nitration has been studied only very slightly from the quantitative standpoint. A great deal of qualitative work has been done and some of the reactions are certainly catalytic although in most cases heterogeneous. It seems therefore desirable to broaden the scope of the discussion of these reactions to include some heterogeneous and photochemical reactions, with the hope that this may throw some light on possible homogeneous catalytic reactions of paraffin hydrocarbons.

Halogenation of Paraffin Hydrocarbons

Hydrocarbons both saturated and unsaturated [4] react with bromine with or without a solid catalyst; the solid catalyst not only influences the rate of halogenation but also determines the initial direction of substitution. This has been shown by Mereshkowsky in a study of the bromination of propylene and butane. There seems to be some ten-

[1] Grignard and Stratford, *Compt. rend.*, **178**, 2149 (1924); see also Pictet and Lerezynska, *Bull. Soc. chim.*, **19**, 326 (1916).
[2] Woog, *Compt. rend.*, **177**, 60, 207 (1923).
[3] Jaeger, *Brennstoff Chem.*, **4**, 259 (1923).
[4] Mereshkowsky, *Ann.*, **431**, 113 (1923); *idem, Bull. Soc. chim.*, **37**, 861 (1925); Kronstein, *Ber.*, **54**, 1 (1921); Blair, Wheeler and Ledbury, *J. Soc. Chem. Ind.*, **43**, 289T (1924); Kokatnur, *J. Am. Chem. Soc.*, **41**, 120 (1919); Schleede and Luckow, *Ber.*, **55**, 3710 (1922).

dency, when solid catalysts are used, for the intermediate stages to be omitted or to occur so rapidly that their presence is unnoticed. Thus Phillips [5] reports that the chlorination of methane under the influence of different solid catalysts gave mainly the first and last substitution products; under similar conditions symmetrical tetrachloroethane gives hexachloroethane, without producing any pentachloroethane.[6] This gives a curious contrast to the results obtained when light is used as catalyst, for the halogen then enters progressively giving all the intermediate products.

Benrath and Hertel [7] studied the photo-chlorination of many alipathic compounds dissolved in carbon tetrachloride. Trichloroethane after an induction period of about 30 minutes absorbs about 70 per cent of the chlorine required for its complete conversion into carbon tetrachloride. On the other hand they report that tetrachloroethane under these conditions is not attacked by chlorine in 3 hours.

A curious reaction occurs [8] when dilute hexane vapor is led into wet bromine. *Para* dibromobenzene and trans-benzene hexabromide are formed, although liquid bromine and liquid hexane give dibromohexane. If benzene vapor is substituted for the hexane vapor the same products are formed and at approximately the same rate. It would be desirable to repeat this work taking additional precaution against the possibility of benzene being present in the hexane.

Datta and Chatterjee [9] obtained a small yield of iodohexane by the action of iodine and nitric acid on liquid hexane. Iodine alone acts on all hydrocarbons, sometimes in the cold, but usually at higher temperatures.[10] The reaction is a complicated one, hydriodic acid being formed and carbon liberated which forms a colloidal solution.

Oxidation of Paraffin Hydrocarbons

Saturated hydrocarbons are readily oxidized by oxygen at higher temperatures either with or without a solid catalyst. Stepski [11] has studied the oxidation of hexane using a platinum catalyst and Wheeler and Blair [12] studied the same process without a catalyst. Aldehydes,

[5] Phillips, *Am. Chem. J.*, **16**, 362 (1894).
[6] Monneyrat, *Compt. rend.*, **126**, 1805 (1896); Kokatnur, *J. Am. Chem. Soc.*, **41**, 120 (1919).
[7] Benrath and Hertel, *Z. wiss. Phot.*, **23**, 30 (1924).
[8] Blair, Wheeler and Ledbury, *J. Soc. Chem. Ind.*, **43**, 289T (1924).
[9] Datta and Chatterjee, *J. Am. Chem. Soc.*, **39**, 439 (1917).
[10] Nellensteyn, *Chem. Weekblad.*, **21**, 102 (1924).
[11] Stepski, *Monatsh.*, **23**, 789 (1902).
[12] Wheeler and Blair, *J. Soc. Chem. Ind.*, **42**, 491T (1923).

ethylene, carbon monoxide, carbon dioxide, and water are the chief products. While these reactions probably are mainly heterogeneous it seems likely that the oxidation of liquid hydrocarbons may be in part homogeneous. This oxidation has been extensively studied [13] not only on account of the scientific interest but also in an attempt to prepare fatty acids for commercial purposes using mostly solid catalysts, although the use of alkalis and alkaline earths suggests the possibility of hydroxyl-ion catalysis. Salway and Williams studied [14] the oxidation of hexadecane using manganese stearate as catalyst and found that fatty acids and hydroxy acids are the main products. The oxidizing action of potassium permanganate on tertiary hydrocarbons has been studied by several authors [15] who found that they undergo oxidation much more rapidly than normal hydrocarbons. This is in line with recent work on heavily substituted derivatives of ethane [16] in which the strength of the carbon-carbon bond can be so diminished that there is a progressive dissociation in solution into two radicals. This weakening of the bond in the case of a carbon-halogen union is shown by Walden's observation that while methyl iodide is comparatively stable, tertiary butyl iodide is ionized in sulfur dioxide solution.

Other Reactions of Paraffin Hydrocarbons

It is well known that nitrogen peroxide can react as an oxidizing agent, and its action on paraffins has been the subject of several investigations.[17] Saturated aliphatic hydrocarbons are but slowly attacked by nitrogen peroxide, fatty acids being first formed which are themselves slowly oxidized to oxalic acid and carbon dioxide; the nitrogen peroxide is reduced to the lower oxides and partly to nitrogen. As is usual with the oxidizing agents, secondary and tertiary paraffins are less resistant than primary paraffins. Nitrosyl chloride oxidizes heptane [18] and the final product on hydrolysis is a mixture of ketones presumably obtained from the corresponding oximes. Nitro derivatives

[13] Grün, Ulrich and Wirth, *Ber.*, **53**, 897 (1920); Fisher and Schneider, *ibid.*, **53**, 922 (1920); Kelber, *ibid.*, **53**, 66, 1567 (1920); Franck, *Chem. Zeit.*, **44**, 309 (1920).

[14] Salway and Williams, *J. Chem. Soc.*, **121**, 1347 (1922).

[15] Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 1788 (1913); Levine and Cretcher, *J. Biol. Chem.*, **33**, 505 (1918); Levine and Taylor, *ibid.*, **54**, 351 (1922).

[16] Gomberg and Schoepfle, *J. Am. Chem. Soc.*, **41**, 1655 (1919); Gomberg, *Ber.*, **37**, 2049 (1919); Schmidlin, *ibid.*, **41**, 2471 (1908); Wieland, *ibid.*, **42**, 3029 (1909); Usherwood, *J. Soc. Chem. Ind.*, **42**, *Chem. and Ind.*, **1**, 1246 (1923); Walden, *Ber.*, **35**, 2029, 2031 (1902).

[17] Gränacher, *Helv. Chem. Acta*, **3**, 721 (1920); Gränacher and Schaufelberger, *ibid.*, **5**, 392 (1922); Schaarschmidt, *Z. angew. Chem.*, **37**, 933 (1924).

[18] Lynn, *J. Am. Chem. Soc.*, **41**, 368 (1919).

of saturated hydrocarbons can be obtained by the direct action of nitric acid on saturated hydrocarbons,[19] but there is more or less oxidation depending on the conditions. Apparently the reaction is autocatalytic because Konowaloff states that the process of nitration is greatly facilitated by the use of nitric acid which has been used in previous experiments.

Aliphatic hydrocarbons readily undergo direct sulfonation.[20] Cold fuming sulfuric acid is without perceptible action upon the pure hydrocarbon and if the temperature is too high, the sulfonic acids first formed are destroyed. The best temperature seems to be the boiling point of the hydrocarbon. By using fuming sulfuric acid only the monosulfonic acid is formed, whereas the use of sulfuric anhydride yields mainly disulfonic acids. Yields of about 40 per cent of the theoretical can be obtained, the rest of the hydrocarbon being oxidized to carbon dioxide and water.

There is a curious contrast between the thermal decomposition of open-chain paraffins and aromatic hydrocarbons or cycloparaffins.[21] Whereas benzene hydrocarbons and cycloparaffins yield much hydrogen on decomposition, open-chain paraffins do not, suggesting that in this case the carbon-carbon bond is weaker than the carbon-hydrogen bond.

It is hardly possible to conclude with any great degree of certainty, from a review of the literature, whether or not homogeneous catalysis enters into the reaction of saturated hydrocarbons. They do however take part in a number of slow homogeneous reactions, and it seems likely that kinetic studies would decide the point as to whether these reactions are affected by any dissolved catalyst.

Halogenation of Ethylene

The reactions of unsaturated hydrocarbons [22] have been much more carefully studied than those of the paraffins and a good deal of quantitative work is now available. Several studies have been made on the simplest unsaturated hydrocarbon, ethylene. In the gas phase Stewart and Edlund [23] studied the reaction with bromine, the object being to find

[19] Konowaloff, *J. Russ. Phys. Chem. Soc.*, **38**, 109 (1906); Worstall, *Am. Chem. J.*, **20**, 202 (1898).
[20] Worstall, *Am. Chem. J.*, **20**, 664 (1898).
[21] Haber, *Ber.*, **29**, 2691 (1896); Bone and Coward, *J. Chem. Soc.*, **93**, 1202, 1211 (1908); Jones, *ibid.*, **107**, 1582 (1915).
[22] See Lapworth and McRae, *J. Chem. Soc.*, **121**, 2741 (1922); Kolkar and Lapworth, *ibid.*, **127**, 307 (1925).
[23] Stewart and Edlund, *J. Am. Chem. Soc.*, **45**, 1014 (1923).

out if there are any active tautomers present which may be represented as follows:

$$H_2\dot{C} : \dot{C}H_2 \qquad H_2C : : CH_2 \qquad H_2\ddot{C} : CH_2$$

The middle form represents the closed double bond whereas the other two represent open double bonds. Assuming the presence of one of these the action with bromine can be represented as

$$H_2C : : CH_2 \rightleftarrows H_2\dot{C} : \dot{C}H_2 \tag{1}$$

$$H_2\dot{C} : \dot{C}H_2 + Br_2 = C_2H_4Br_2 \tag{2}$$

If reaction (1) is slow and (2) very rapid a kinetic study will show a unimolecular reaction independent of the bromine concentration; if reaction (1) is very rapid and (2) slow a kinetic study will show a bimolecular reaction whose rate is proportional to the ethylene concentration and to the bromine concentration. Similar but more complicated results should be obtained if both electromers are present.

The experimental results obtained showed that the rate of the complete reaction is proportional to the concentrations of both the ethylene and bromine, but it is also proportional to the surface-volume ratio of the containing vessel. The authors concluded that very little if any reaction takes place in the gas phase, even in presence of water vapor. With a constant surface, the reaction rate is proportional to the concentrations of both ethylene and bromine, and no evidence was obtained of a unimolecular reaction or any deviation from a bimolecular reaction. If the reaction of ethylene takes place through dissociation or opening of the double bond, such a change does not take place appreciably in the compound *of itself,* but rather under the influence of surface or solvent.

These experiments were confirmed and extended by Norrish,[24] who investigated the reaction rate between dry ethylene and dry bromine in a glass vessel whose walls were coated with various substances. The rate was found to be completely dependent upon the polarity of the substance used to cover the glass. A polar substance like stearic acid gave a reaction rate greater than when glass walls were used. Cetyl alcohol on the walls greatly diminished the rate, and for paraffin wax the rate was extremely slow. In one experiment 4 liters of air containing 2 per cent bromine and 2 per cent ethylene were passed slowly through two similar tubes in series kept at 0°; at the end of the

[24] Norrish, *J. Chem. Soc.,* **123**, 3006 (1923).

experiment, the first tube, which was paraffined, contained no ethylene dibromide while 0.25 gram collected at the bottom of the second tube, which was of uncoated glass. It is evident therefore that the halogenation of double bonds is a catalytic phenomenon and that reaction can only be brought about by collision with a catalyst in either the gaseous, liquid or surface phase. Stewart and Fowler [25] have measured the rate of reaction between ethylene and chlorine and find that it is also purely a wall reaction, the rate of which is proportional to the surface-volume ratio. In some of their experiments the shape of the concentration-time curve suggested that the reaction is catalytic. They criticize some of the conclusions of Norrish and point out that liquid ethylene bromide catalyzes the reaction. This liquid does not readily wet a paraffin surface, which may account for the low velocity in a paraffin-covered vessel.

These results indicate that previous results on the reaction rates of halogens and ethylene compounds may be wholly or in part wall reactions or catalyzed by accidental impurities present. Plotnikow [26] studied the rate of addition of bromine to ethylene in ligroin solution at low temperatures, —78° to —100°. The combination takes place with contraction and this was used to measure the velocity. He found a slow bimolecular reaction accompanied by unexplained initial irregularities. The reaction had a high temperature coefficient, 6.2 for 10°.

Halogenation of Ethylene Linkage

Sudborough and Thomas [27] have studied the rate of addition of bromine to the ethylene linkage of unsaturated organic compounds in carbon tetrachloride solutions. They found these reactions to be bimolecular, practically non-reversible, and very sensitive to light, ordinary diffused daylight raising the value of the constant by one or more orders. Table XVI gives some of the results for different unsaturated acids and esters; the experiments were conducted in the dark with equimolar quantities of bromine and organic compound and the velocity constant was calculated from the formula $k = 1/t \cdot x/a(a - x)$; the values obtained for the velocity constant are not very concordant and vary from 50 per cent to 100 per cent.

[25] Stewart and Fowler, *J. Am. Chem. Soc.*, **48**, 1187 (1926).
[26] Plotnikow, *Z. physik. Chem.*, **53**, 605 (1905).
[27] Sudborough and Thomas, *J. Chem. Soc.*, **97**, 715, 2450 (1910). See also Herz and Myline, *Ber.*, (a) **39**, 3816 (1906); (b) **40**, 2898 (1907); Barrett and Lapworth, *Proc. Chem. Soc.*, **23**, 18 (1907); Hofmann and Kirmreuther, *Ber.*, **42**, 4481 (1909).

TABLE XVI

VELOCITY CONSTANTS FOR THE ADDITION OF BROMINE TO UNSATURATED ORGANIC ACIDS IN CARBON TETRACHLORIDE SOLUTION.[a]

Organic Acid		k (± 50%)
Crotonic	$CH_3CH:CHCOOH$	2×10^{-5}
Cinnamic[b]	$C_6H_5CH:CHCOOH$	2×10^{-4}
β-Ethyl Acrylic	$C_2H_5CH:CHCOOH$	4×10^{-5}
Phenyl $\beta\gamma$-Crotonic	$C_6H_5CH:CHCH_2COOH$	5
Allyl Acetic	$CH_2:CHCH_2CH_2COOH$	2×10^{3}
Ethylidene Propionic	$CH_3CH:CHCH_2COOH$	50
Undecylenic	$CH_2:CH(CH_2)_8COOH$	1
Oleic	$CH_3(CH_2)_7CH:CH(CH_2)_7COOH$	31
Elaidic	$CH_3(CH_2)_7CH:CH(CH_2)_7COOH$	11
Sorbic	$CH_3CH:CHCH:CHCOOH$	4×10^{-3}
Cinnamylidene Acetic	$C_6H_5CH:CHCH:CHCOOH$	2×10^{-3}

[a] The results for the velocity constants have been rounded off to facilitate comparison.

[b] The methyl and ethyl esters give the same velocity constant as the acid.

The velocity constants are possibly arbitary, being determined by the presence of some catalyst in unknown amount, a possibility which the authors recognize, for they state: "The compounds used in these experiments were all purified before use. The values of k obtained for any given compound are not very concordant. . . . The only reason we can offer is that a trace of some impurity has a considerable effect on the velocity of the reaction." When they used different samples of bromine and carbon tetrachloride the velocity of bromination of cinnamic acid changed by a whole order, and they were unable to ascertain the reason for this. In spite of the arbitrary values of these constants they are probably comparable and show that the addition of bromine to $\alpha\beta$-unsaturated acids is a comparatively slow process. When the double bond is further removed from the carboxyl group the addition is very rapid and is completed in the course of a few minutes. Bromine adds to sorbic acid and cinnamylideneacetic acid in the $\alpha\delta$ positions and at a greater rate than if only the $\alpha\beta$-double bond were present.

A recent study [28] suggests that halogenation of the ethylene linkage is catalytic when the reaction occurs in solution. Iodine in chloroform solution adds slowly to hydrocarbons containing a double bond, the reaction being of the second order. Apparently a minute trace of iodine chloride acts catalytically, because a fresh solution of iodine in chloroform reacts more slowly than one which has been prepared for some days. The authors found that when a benzene nucleus is at-

[28] Böeseken and Blumberger, *Rec. trav. chim.*, **44**, 96 (1925).

tached near the double bond the rate of iodination is slow. Brüner and Fischler [29] found that the addition of chlorine and bromine to ethyl cinnamate in carbon tetrachloride solution is strongly catalyzed by the addition of iodine. Various metallic bromides were also found to be catalytic in these reactions. The addition of an ester of hypobromous acid to an olefinic linkage [30] occurs readily in the presence of acids and bromotrinitromethane.

Recently [31] another attempt has been made to test the prediction of the electronic interpretation of the ethylenic linkage, that there are active tautomers present, probably in small quantity.[32] The authors tested the action of organo-magnesium halides on numerous substituted ethylenic compounds. They found that there was no reaction and concluded that if there were any active or polar forms of the ethylene linkage they are present in extremely small amount or are not sufficiently active to add RMgX compounds.

Addition of Halogen Acids to Ethylene Linkage

Maass and co-workers [33] have studied the addition of hydrobromic acid to unsaturated hydrocarbons. In one paper the system allylene-hydrobromic acid was studied and found to give an equimolecular compound. The freezing-point curve for the system acetylene-hydrobromic acid showed no indication of compound formation. On allowing mixtures of allylene and acid to warm up, addition took place but mixtures of acetylene and acid did not react even when kept for a considerable time at room temperature.

Similar behavior was observed [34] for the mixtures propylene-hydrobromic acid and ethylene-hydrobromic acid. Figure 11 shows the curves obtained. The propylene-hydrobromic acid curve shows that these components have a greater tendency to compound formation, and it was found that they reacted quickly at room temperature and rela-

[29] Brüner and Fischler, *Z. Elektrochem.*, **20**, 84 (1914).
[30] Schmidt, Schumacher and Asmus, *Ber.*, **56**, 1239 (1923).
[31] Gilman and Peterson, *J. Am. Chem. Soc.*, **48**, 423 (1926).
[32] Lewis, *J. Am. Chem. Soc.*, **38**, 762 (1916); also "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, **1923**, p. 124; and *Trans. Faraday Soc.*, **19**, 452 (1923); Lowry, *J. Chem. Soc.*, **123**, 822 (1923); *idem, Trans. Faraday Soc.*, **19**, 488, 497, 536 (1923); Carothers, *J. Am. Chem. Soc.*, **46**, 2266 (1924); Robinson and Robinson, *J. Chem. Soc.*, **123**, 532 (1923); Eastman, *J. Am. Chem. Soc.*, **44**, 438 (1922); Noyes, *ibid.*, **45**, 2950 (1923); Lapworth, *J. Chem. Soc.*, **121**, 416 (1922); Kermack and Robinson, *ibid.*, **121**, 427 (1922); Kolker and Lapworth, *ibid.*, **127**, 307 (1925); Ingold and Weaver, *ibid.*, **125**, 1456 (1924); Hojendahl, *ibid.*, **125**, 1381 (1924).
[33] Maass and Russell, *J. Am. Chem. Soc.*, **43**, 1227 (1921).
[34] Maass and Wright, *J. Am. Chem. Soc.*, **46**, 2664 (1924).

tively slowly at —78°. Ethylene and hydrobromic acid do not react. The rate of combination of propylene and hydrobromic acid in a 1:1 molecular mixture was measured at two temperatures, —78° and 0°. During the first half of the reaction the percentage of hydrobromic acid combined is proportional to the time, after which the reaction slows up. Combination ceases when a certain fraction of the hydrobromic acid combines, 71 per cent at —78° and 89 per cent at 0°;

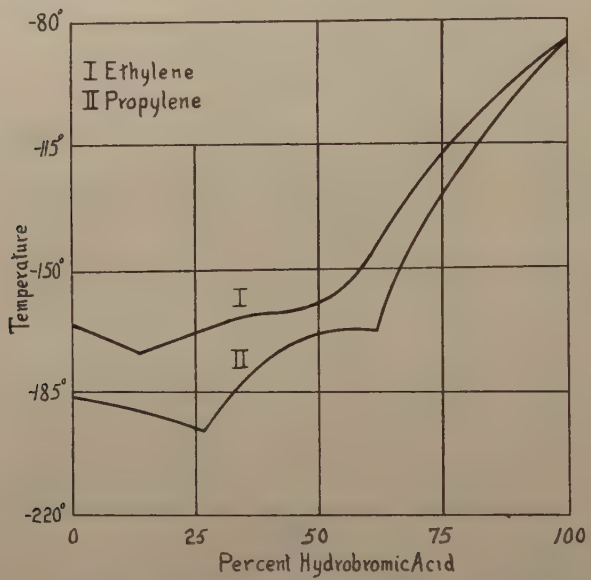


FIG. 11.—System: Unsaturated Hydrocarbon—Hydrobromic Acid.

this fraction depends on the temperature but is not due to an equilibrium between propylene and hydrobromic acid. The authors show that three simultaneous reactions take place, the main reaction being formation of *iso*-propyl bromide. The secondary reactions are formation of normal-propyl bromide, a reaction represented by the following equation in which one or more bromohexanes are formed:

$$2CH_3CH : CH_2 + HBr = C_6H_{13}Br.$$

The last reaction accounts for the presence of uncombined hydrobromic acid in the 1:1 mixtures.

The interpretation advanced [35] by the authors to explain the rela-

[35] For the mode of attachment of halogen hydrides to isoprene see Claisen, Kremers, Roth and Tietze, *J. pr. Chem.*, **105**, 65, 288 (1922).

tive reactivity of propylene and ethylene is as follows: " . . . the molecular attraction of propylene for hydrogen bromide as indicated by freezing point measurements is greater than that of ethylene for hydrogen bromide. Molecular attraction tends to keep molecules together for a sufficient length of time to allow interatomic changes to take place. Violent collision may be required in order to cause the atomic vibrations in a molecule necessary for the reaction but this must be followed by the continued close proximity of the two reacting molecules. The attraction between propylene and hydrogen bromide molecules as such is sufficiently great to cause a large number of pairs to be available for such a process. It follows that the velocity of the reaction between propylene and hydrogen bromide will be much greater than that between ethylene and hydrogen bromide where the molecular attraction is much less."

In view of the results for the addition of bromine to ethylene compounds it would be interesting to know if the addition of hydrobromic acid to propylene is also a catalytic phenomenon which would not occur if the reaction took place in a vessel with non-polar walls. Assuming this to be the case, the results indicate that the propylene reaction is much more easily catalyzed than the ethylene reaction, since in a 1 : 1 : 2 molecular mixture of ethylene, propylene and hydrobromic acid only the propylene reacted.

Ethylene and Halogens in Aqueous Solution

The reaction between ethylene and halogens in aqueous solutions follows an entirely different course from the reaction in organic solvents and under certain conditions yields practically pure ethylene chlorohydrin or bromohydrin.[36] The action is the same for both chlorine and bromine and may be represented in the case of chlorine by the following equation,

$$\underbrace{H_2O + Cl_2}_{\downarrow\uparrow\ \underbrace{HCl + HClO}} + C_2H_4 \rightarrow C_2H_4Cl_2 + H_2O$$

$$HCl + HClO + C_2H_4 \rightarrow C_2H_4(OH)Cl + HCl.$$

The ethylene and chlorine may be passed into the water at a very rapid rate and at low temperatures (0° to 20°), and concentrations as high as 15 per cent of chlorohydrin may be obtained. In the early

[36] Gomberg, *J. Am. Chem. Soc.*, **41**, 1414 (1919); Read and Williams, *J. Chem. Soc.*, **111**, 240 (1917); Read and Hook, *ibid.*, **117**, 1214 (1920); Read and Hurst, *ibid.*, **121**, 989 (1922).

stages the molecular ratio of bromohydrin to dibromide is about 20: 1, but this falls somewhat as the reaction proceeds. The reaction does not seem to be markedly affected by catalysts although Read and Hook note: "In other series of experiments the corresponding times were noticeably different, and it seems possible that the acceleration or retardation was due to the presence of small amounts of foreign substances."

It may be noted that chlorohydrins may also be prepared from ethylenic hydrocarbons by means of monochlorocarbamide, which readily combines with olefines in the presence of dilute acetic acid to give the corresponding chlorohydrins;[37] the monochlorocarbamide is obtained by chlorinating urea in aqueous solution.

Oxidation of the Ethylene Linkage

The oxidation of ethylene both by oxygen[38] and by ozone[39] has been carefully studied. When oxygen is used the reaction is slow and proceeds apparently in the homogeneous gas condition, but is also affected by a variety of solid catalysts. This first stage is assumed to be the oxidation of one of the hydrogens to hydroxyl to give vinyl alcohol, which immediately rearranges to acetaldehyde. There does not appear to be any evidence of catalytic action in the homogeneous reaction. Ozone adds directly to the ethylene to give an ozonide, which can decompose to give formaldehyde and formic acid, or hydrolyze to formaldehyde and hydrogen peroxide. It would be interesting to test if the addition of ozone is similar to the addition of bromine which takes place only in the presence of polar walls.

Hydrogen peroxide[40] under the influence of the hydroxyl ion oxidizes the double bond in compounds of the type

$$R_2C = \overset{R}{\underset{|}{C}} - \overset{R}{\underset{|}{C}} = O.$$

The ethylene group alone, di-olefines, and $\alpha\beta$-unsaturated acids are relatively stable under these conditions.

[37] Detoeuf, *Bull. Soc. chim.*, **31**, 102, 169, 176 (1922).
[38] Willstätter and Bommer, *Ann.*, **442**, 36 (1921); Blair and Wheeler, *J. Soc. Chem. Ind.*, **41**, 303T (1922).
[39] Harries, *Ber.*, **37**, 839 (1904); *idem, ibid.*, **42**, 3305 (1909); *idem, Ann.*, **343**, 311 (1905).
[40] Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).

Nitration of Unsaturated Aliphatic Hydrocarbons

The action of nitric acid on unsaturated aliphatic hydrocarbons has been the subject of a number of papers.[41]. Wieland and his co-workers have studied the action of nitric acid on ethylene and its derivatives and have shown that ethylene can be nitrated directly to ethylene dinitrate and to β-nitroethyl nitrate; this is converted by phosphorus pentoxide to nitroethylene. Anschütz and Hilbert studied the course of the nitration of diphenylethylene in glacial acetic acid, which occurs as follows;

$$(C_6H_5)_2C:CH_2 \xrightarrow{HNO_3} (C_6H_5)_2C(OH)CH_2NO_2 \rightarrow (C_6H_5)_2C:CHNO_2 + H_2O$$

$$(C_6H_5)_2C:CHNO_2 \xrightarrow{HNO_3} (C_6H_5)_2C(OH)CH(NO_2)_2 \rightarrow (C_6H_5)_2C:C(NO_2)_2 + H_2O.$$

The second, third and last compounds were isolated.

Recently the action of nitric acid on acetylene has been investigated by Orton and McKie [42] who find that acetylene is absorbed with great ease by absolute nitric acid or mixtures of nitric acid and sulfuric acid; dilution of the nitric acid diminished the rate of interaction. The products of the interaction of acetylene and nitric acid are various and are determined by the concentration of the acid, by the temperature and by the presence of a catalyst or of sulfuric acid; usually nitroform is the principal product of the reaction (75%-85%). Various metallic salts were tried as catalysts but practically all of these except mercury favor oxidation of the acetylene at the expense of the production of nitroform. Mercury alone causes a marked increase in the production of nitroform and at the same time simplifies the reaction so that the acetylene is quantitatively represented by nitroform and carbon dioxide.

The addition of nitrogen trichloride to olefine hydrocarbons in carbon tetrachloride has recently been studied.[43] With 2-butene the reaction takes place fairly rapidly with formation of a moderate yield of 2-chloro-3-dichloroaminobutane, $CH_3CHNCl_2CHClCH_3$. The possible effect of catalysts on the reaction has not yet been investigated.

[41] Wieland and Sakellarios, *Ber.*, **53**, 201 (1920); *idem, ibid.*, **52**, 898 (1919); Wieland and Rahn, *ibid.*, **54**, 1770 (1921); Anschütz and Hilbert, *Ber.*, **54**, 1854 (1921).

[42] Orton and McKie, *J. Chem. Soc.*, **117**, 283 (1920).

[43] Coleman and Howells, *J. Am. Chem. Soc.*, **45**, 3084 (1923).

Sulfonation of Ethylene

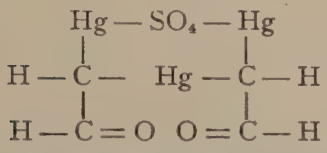
Ethylene reacts rapidly with sulfuric acid to give ethyl hydrogen sulfate and diethyl sulfate. The action is catalyzed [44] by various metallic sulfates particularly silver sulfate. Plant and Sidgwick [45] find that the ethyl sulfuric acid has a distinct autocatalytic effect,[46] but attribute this to the greater solubility of ethylene in the liquid phase as ethyl sulfuric acid accumulates in the system.

Hydration of Acetylene

The conversion of acetylene to acetaldehyde by passing into an aqueous solution of a mercury salt has been studied by Vogt and Nieuwland.[47] Mercuric sulfate in dilute sulfuric acid solution was found to be the most suitable catalyst owing to its activity and the lasting qualities of the catalytic solution. The actual catalyst is apparently a compound of acetylene with a basic salt of the mercury. It does not seem likely that the inorganic salts of mercury act as carriers of acetylene, because it was not possible to detect any inorganic salts of mercury in any of the catalytic mixtures after absorption of acetylene. Many mercury salts in acid solution absorb acetylene rapidly for a short time, forming a precipitate, and such solutions absorb acetylene only very slowly after the initial reaction is over. On the other hand, if the acetylene compound of the salt is soluble in the corresponding acid the solution continues to absorb acetylene for a long time.

A side reaction occurs in this catalytic process in which the mercury salt is reduced to metallic mercury; this appears to be due to the action of the acetylene or acetaldehyde on hydrolyzed mercury compounds. The catalytic action here is evidently association of acetylene and water through the mercury salt followed by interaction to give acetaldehyde. The structure of these mercury salts is therefore of considerable interest but owing to their complexity is very uncertain. The precipitate obtained by treating mercuric acetate in dilute acetic acid with acetylene has the empirical formula [48] $3HgO.2C_2H_2$, and Vogt and Nieuwland assume that the precipitate from mercuric sulfate solutions is the sulfate of the same radical of which the precipitate from mercuric acetate is the oxide. The following structural formula is suggested as a possibility:

[44] Gluud and Schneider, *Ber.*, **57**, 254 (1924). See also Evans and Albertson, *J. Am. Chem. Soc.*, **39**, 456 (1917).
[45] Plant and Sidgwick, *J. Soc. Chem. Ind.*, **40**, 14T (1921).
[46] The same effect has been noted for chlorosulfonic acid. See Traube and Justh, *Brennstoff Chem.*, **4**, 150 (1923); Damiens, *Compt. rend.*, **175**, 585 (1922).
[47] Vogt and Nieuwland, *J. Am. Chem. Soc.*, **43**, 2071 (1921).
[48] Plempton, *Chem. News*, **65**, 295 (1892).



Adams, Roman and Sperry [49] give a good discussion of the structure of the compounds produced from olefines and mercury salts.

We may conclude this survey of the reactions of saturated and unsaturated aliphatic hydrocarbons by stating that they are nearly always sensitive to heterogeneous catalysts and in some of the examples investigated they are affected by homogeneous catalysts. The comparatively small amount of quantitative work done in this field makes it difficult to estimate to what extent homogeneous catalysts affect these reactions.

[49] Adams, Roman and Sperry, *J. Am. Chem. Soc.*, **44**, 1781, 2968 (1922).

Chapter VIII.

Reactions of Benzene and Derivatives.

The study of rates of reactions in which one of the reacting substances is a benzene derivative has been inspired by a desire to displace the old qualitative rules for the substitution of hydrogen atoms of the benzene ring. Shortly after Kekulé in 1865 had suggested his benzene formula, Körner [1] gave rules governing the entrance of a new substituent in the benzene nucleus. Körner as well as other early workers [2] concluded that acid groups direct a new substituent to the *meta*-position, whereas the halogens, the hydroxyl group, and basic groups direct to the *ortho-para*-positions. Armstrong, Crum-Brown and Gibson, Vorländer [3] and others put forward extensions of the original rules.

Physical Properties and Directive Influence

Recently J. J. Thomson [4] has suggested a possible connection between directive influence and dielectric capacity, and Rule and Patterson [5] have pointed out possible relations between dielectric capacity, optical activity and ionization constants of the substituted benzoic acids. Since there is great difficulty in making such comparisons owing to the lack of systematic reliable data on a series of organic compounds, a comparison [6] has been made recently of melting-points of a series of organic compounds of the general formula C_6H_5X and the directive influence of the group X. A similar comparison was made for disubstituted benzene derivatives C_6H_4XY and in both cases there is a parallel progression. The boiling-points show a precisely similar regularity but the differences are not so great since [7] vapor pressure and solubility relations of the liquid state are, in the majority of benzene derivatives,

[1] Körner, *Gazz. Chim. Ital.*, **4**, 305, 446 (1874).
[2] Hübner, *Ber.*, **8**, 873 (1875); Nölting, *ibid.*, **9**, 1797 (1876).
[3] Armstrong, *J. Chem. Soc.*, **51**, 258 (1887); Crum-Brown and Gibson, *ibid.*, **61**, 367 (1892); Vorländer, *Ann.*, **320**, 122 (1902).
[4] J. J. Thomson, *Phil. Mag.*, **46**, 497 (1923).
[5] Rule and Patterson, *J. Chem. Soc.*, **125**, 2155 (1924).
[6] Francis, Andrews and Johnston, *J. Am. Chem. Soc.*, **48**, 1624 (1926).
[7] Sidgwick and Callow, *J. Chem. Soc.*, **125**, 529 (1924).

very slightly influenced by the orientation of the substituents, whereas the solubility of solids is largely determined by the crystalline forces, which themselves are largely affected by the orientation. The two divisions made by Francis, Andrews and Johnston are (1) *meta* controlling groups, which include all derivatives of quinquivalent nitrogen, hexavalent sulfur, $-CO-$, $-CN$, and $-CCl_3$; (2) *ortho-para* controlling groups, which include all derivatives of trivalent nitrogen, bivalent sulfur, the halogens, $-O-$, $-CH-$ (except $-CHO$ and $-CHN-$), and $-C_6H_5$ and its derivatives. This study brings out the point that of the three isomers of a simple compound of the type C_6H_4XY, the *para* isomer has the highest melting-point, independent of the character of X and Y, whereas the melting-points of the *ortho* and *meta* isomers depend on the directive influence of these two groups. If they are alike the melting-point of the *meta* compound is usually the lower whereas if they are unlike that of the *ortho* is usually lower.[8] Since the *para* compound has the highest melting-point we may interpret this as a consequence of its being most "symmetrical."

The authors then indicate a possible relation between this and chemical reactivity: "May one, on this basis, argue that the *ortho* or the *meta,* according as one or the other melts lower, is the least symmetrical, and if so, may one combine this idea with the rule discussed above and hazard the statement that, of the two isomers, that which reacts more readily (as a liquid) is the less symmetrical, thus relating the directive effect of the groups to the degree of symmetry of the compound? The main difficulty in making a test of this speculation would lie in assigning a degree of "symmetry," which might be chosen either as a geometrical concept (if the crystallographic data were available) or, perhaps preferably, as equivalent to degree of polarity and associated, therefore, with the lack of uniformity of the electric field about the molecule. This is suggested by the fact that the melting temperature of a typical non-polar compound such as methane is lower than that of similar polar compounds such as ammonia or water. On the other hand, we must recognize that melting temperature is not a function of the crystal structure alone, but depends also upon the constitution of the liquid in contact with the crystals, although, in the case of pure liquids, the constitution is again determined by the molecular forces."

[8] See also Pastak, *J. Chim. phys.,* **22**, 48, 264 (1925) for a further discussion of these relations.

Substitution in Benzene Derivatives

The various rules given by different authors are more or less inadequate and are sometimes in contradiction to each other. The inadequacy of the original rules may be seen by considering a study of the nitration of phenylnitromethane.[9] If instead of the *nitro* derivative we have the *chloro, cyano,* or *carboxyl* derivative, nitration yields *ortho-para*-derivatives, from which it might be inferred that the phenylnitromethane would also give *ortho-para*-derivatives. Investigations, however, showed that it belongs to the *meta*-series. Similar instances abound, so that it becomes difficult to express in clear terms how a group which is present will direct a new entering group.

Holleman[10] was the first to recognize that the problem could be studied from the kinetic standpoint and he has published the results of many extensive investigations. When a monosubstituted benzene derivative reacts with a second substance to produce a disubstituted benzene derivative, the new group can enter one of three positions. The actual mechanism consists therefore of three side reactions, the relative velocities of which determine the relative amounts of products. Table XVII shows the results obtained by nitrating a series of

TABLE XVII

THE NITRATION OF VARIOUS MONOSUBSTITUTED BENZENE DERIVATIVES

Compound	*Ortho* Per Cent	*Meta* Per Cent	*Para* Per Cent
C_6H_5F	12.4	trace	87.6
C_6H_5Cl	30.1	"	69.9
C_6H_5Br	37.6	"	62.4
C_6H_5I	41.1	"	58.7
$C_6H_5CH_3$	58.8	4.4	36.8
$C_6H_5CH_2Cl$	40.9	4.2	54.9
$C_6H_5CHCl_2$	23.3	33.8	42.9
$C_6H_5CCl_3$	6.8	64.5	28.7
$C_6H_5NO_2$	6.4	93.2	0.25
C_6H_5COOH	18.5	80.2	1.3
$C_6H_5COOC_2H_5$	28.3	68.4	3.3

compounds. It will be seen that there is no sharp distinction between *ortho-para-* and *meta*-directing groups. It is possible to cause a large variation in the relative quantities of the isomerides as is shown by the successive chlorination of the methyl group in toluene.

[9] Holleman, *Rec. trav. chim.*, **14**, 123 (1895).
[10] See Holleman, *Chem. Reviews*, 1, 187 (1924) for a summary of his work.

In the reactions of monosubstituted benzene derivatives we hardly ever find a single reaction occurring without the presence of side reactions also. There are no examples known in which only a pure *ortho*-derivative or a pure *meta*-derivative is obtained, and only a very few examples, such as the sulfonation of the halogen benzenes, which give only the *para*-compound. Pure *ortho-para* substitution without the formation of any *meta*-compound is also extremely rare, possibly non-existent, because none of the methods used would detect the presence of 0.5 per cent of the *meta*-compound.

We may therefore consider all the reactions of monosubstituted benzene derivatives to consist, in the first stage, of three simultaneous reactions, side reactions, whose relative velocities determine the relative yields of the three disubstituted derivatives. These relative velocities are determined by the nature of the group present in the monosubstituted benzene, the nature of the entering group, the nature of the catalyst used, solvent and temperature. It may be noted here that if the five available positions in a monosubstituted benzene derivative were all equally susceptible to attack we would expect the percentage yields of *ortho, meta* and *para* to be 40, 40 and 20 respectively. It is common to refer to substitution as being of the *ortho-para* type when more than 60 per cent of the *ortho-para*-compound is produced, and as the *meta* type when more than 40 per cent of the *meta*-compound is produced. In general the type produced is determined largely by the group already present in the benzene nucleus, but the character of the entering group determines to a considerable extent the relative proportions of the isomers within the type. This is illustrated in Table XVIII.

TABLE XVIII

EFFECT OF ENTERING GROUP ON RELATIVE PROPORTIONS OF ISOMERS

Reaction	*Ortho* Per Cent	*Meta* Per Cent	*Para* Per Cent
$C_6H_5Cl \rightarrow C_6H_4Cl_2$[a]	39.0	6.0	55.0
$C_6H_5Cl \rightarrow C_6H_4ClBr$[a]	11.2	1.6	87.2
$C_6H_5Cl \rightarrow C_6H_4ClNO_2$	30.1	0	69.9
$C_6H_5Cl \rightarrow C_6H_4ClSO_2OH$	0	0	100.0
$C_6H_5Br \rightarrow C_6H_4BrCl$[a]	41.5	6.0	52.5
$C_6H_5Br \rightarrow C_6H_4Br_2$[a]	13.1	1.8	85.1
$C_6H_5Br \rightarrow C_6H_4BrNO_2$	37.6	0	62.4
$C_6H_5Br \rightarrow C_6H_5BrSO_2OH$	0	0	100.0

[a] Iron catalyst used.

Temperature and Benzene Substitution

The effect of temperature is not very marked in halogenations and nitrations, but it has a marked effect on sulfonation,[11] the results for toluene being given in Table XIX. Holleman and Caland suspected

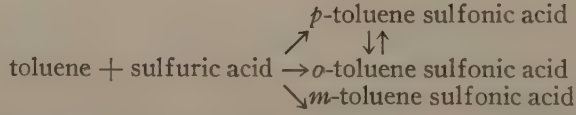
TABLE XIX

EFFECT OF TEMPERATURE ON SULFONATION OF TOLUENE

	0° Per Cent	35° Per Cent	75° Per Cent	100° Per Cent
Ortho	42.7	31.9	20.0	13.3
Meta	3.8	6.1	7.9	8.0
Para	53.5	62.0	72.1	78.7

that the large variations might be due to the transformation of the isomers into each other, but the results showed that there is not formed primarily one toluene sulfonic acid which is afterwards transformed into its isomerides. The *meta*-acid undergoes no change and the *ortho*- and *para*-acids can only be transformed into each other at 100° in the presence of a large excess of sulfuric acid: The reciprocal transformation of these two acids below 75° is so extremely slow as to be negligible.

We may represent the sulfonation of toluene therefore by the following scheme:



The actual mechanism of these sulfonation reactions is probably (1) double compound formation with the sulfuric acid, which is a very rapid reaction, followed by (2) collision of the double compound with hydrogen ion resulting in rearrangement with loss of water to give the sulfonic acid. We have already seen that sulfuric acid very readily forms addition compounds with many organic substances. The evidence shows that combination is extensive so that the compounds probably have a considerable heat of formation and their concentration therefore might be expected to vary appreciably with the temperature; hence the ratios of the sulfonic acids produced might also be expected to vary.

[11] Holleman and Caland, *Ber.*, **44**, 2504, 2519 (1911).

Solvent and Benzene Substitution

There is little evidence available as to the effect of solvent on benzene substitution. Holleman and Rinkes [12] showed that if phenol was brominated either without solvent or in carbon disulfide, acetic acid, or carbon tetrachloride, the relative proportions of isomers was not much affected. The reaction in aqueous solution is quite different.[13] The effect of water is shown also in the nitration of aniline and its derivatives; [14] this influence however does not exist in the nitration of nitrobenzene or of the halogen benzenes. The degree of saturation of a solute in a solvent affects the rate of reaction [15] so that reactivity is closely related to thermodynamic activity. Francis,[16] from a study of certain ionic reactions, concludes that "the reactivity of a dissolved substance is increased by a change in environment in a direction which would tend to throw it out of solution."

Catalysts and Benzene Substitution

The influence of catalysts is usually marked, especially if solid or colloidal catalysts are used. Van der Laar [17] gives a summary of previous work and the results of his study of the bromination of toluene in presence of various catalysts. He found no very marked differences except that ferric bromide and aluminium bromide prevented any bromination of the methyl group. Another study [18] may be quoted in which the introduction of chlorine and bromine into chlorobenzene and bromobenzene was studied. Table XX shows the results of one typical set of experiments.

TABLE XX

BROMINATION OF CHLOROBENZENE

Catalyst	Temperature	*Ortho* Per Cent	*Meta* Per Cent	*Para* Per Cent
None	130°	17.5	1.2	81.3
$AlBr_3$	55°	15.0	9.0	76.0
$FeBr_3$	55°	11.0	1.5	87.5

[12] Holleman and Rinkes, *Rec. trav. chim.*, **28**, 408 (1909).
[13] Francis, Hill and Johnston, *J. Am. Chem. Soc.*, **47**, 2211 (1925).
[14] Holleman, Hartogs and van der Linden, *Ber.*, **44**, 713 (1911).
[15] Dimroth, *Ann.*, **377**, 131 (1910); Bugarsky, *Z. physik. Chem.*, **71**, 750 (1910).
[16] Francis, *J. Am. Chem. Soc.*, **48**, 662 (1926).
[17] van der Laar, *Rec. trav. chim.*, **26**, 1 (1907).
[18] Holleman and van der Linden, *Rec. trav. chim.*, **30**, 305 (1911).

Chlorination of Benzene

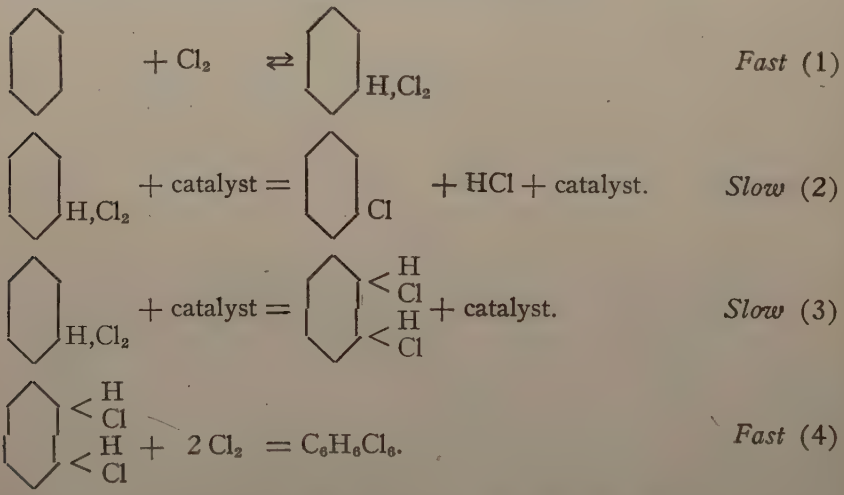
Slator[19] has studied the reaction occurring when a catalyst is added to a dilute solution of chlorine in benzene. In the absence of catalyst no reaction occurs in the dark, but stannic chloride and ferric chloride catalyze the substitution reaction:

$$C_6H_6 + Cl_2 = C_6H_5Cl + HCl.$$

Iodine chloride catalyzes both this reaction and the addition reaction,

$$C_6H_6 + 3\,Cl_2 = C_6H_6Cl_6,$$

the ratio of the substitution reaction to the addition reaction being 7 : 3. Both reactions can be conveniently followed by titrating both the chlorine and the hydrochloric acid. Slator found that the distribution of halogen between the two reactions remains constant for different concentrations of chlorine and iodine chloride; he concludes from this that the addition and substitution are connected in such a manner that the velocity measured, which is the rate of disappearance of chlorine, is the velocity of a single reaction and not that due to two independent changes. It seems more likely however that we have two side reactions and that the action may be represented as follows:



Stannic chloride and ferric chloride catalyze reaction (2) only, so that no benzene hexachloride is formed with these catalysts. Instead of carrying out the reaction in pure benzene solution, the benzene and chlorine may be dissolved in carbon tetrachloride, which merely acts

[19] Slator, *J. Chem. Soc.*, **83**, 729 (1903).

as a diluent; the rate of the reaction is proportional to the concentration of benzene, chlorine and catalyst. When iodine chloride is used the velocity is proportional to the square of the catalyst.

Reactions of Disubstituted Benzene Derivatives

The reactions of disubstituted benzene derivatives have been studied from the kinetic standpoint, with the object of determining the rules governing the position taken by the entering group. An early statement by Beilstein [20] can hardly be described as very helpful: "If a substituent C enters into a compound C_6H_4AB, both A and B exert an influence, but the group (A or B) whose influence predominates directs C to the place it will occupy." Holleman [21] has suggested that if we knew the velocities of the two reactions,

$$C_6H_5A + C = C_6H_4AC$$

and

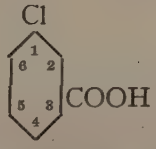
$$C_6H_5B + C = C_6H_4BC,$$

we might be able to predict the course of the reaction

$$C_6H_4AB + C = C_6H_3ABC$$

and the ratio of the isomerides formed. He assumes in this postulate that A and B keep their "directing influence" when the second substituent is introduced, or that the "directing influence" of each is changed in the same proportion.

Actual experiments [22] have shown that it is possible to make predictions of a semi-quantitative kind. By considering compounds of the type,



where the chlorine is *ortho-para*-directing and the carboxyl group is *meta*-directing, we find that in all compounds of this type no substitution occurs at the *meta*-position 5, the compounds formed having the new substituent at positions 2, 4 and 6. We may therefore consider

[20] Beilstein, Handbuch der organischen Chemie, II, 10 (3rd edition).
[21] Holleman, "Die directe Einführung von substituenten in der Benzolkern," Leipzig, 1910.
[22] Wibaut, *Rec. trav. chim.*, **32**, 244 (1913); *idem, ibid.*, **34**, 241 (1915); Holleman, Vermeulen and de Mooy, *ibid.*, **33**, 1 (1914); Holleman, *ibid.*, **34**, 204 (1915).

that the rate of substitution at *ortho-para* positions is very much more rapid than at *meta* positions.

Chlorinating either of the chlorotoluenes gives mainly compounds in which the new substituent is in the *ortho* or *para* position relative to the chlorine; we may conclude therefore that chlorine has a greater directive force than the methyl group, or in other words that the chlorine causes a greater velocity of substitution. If however we introduce a third group into the chlorophenols, we find that the hydroxyl group directs the entering substituent exclusively *ortho-para* to itself, from which we may infer that the hydroxyl group induces a much greater velocity of substitution than chlorine.

Holleman and his pupils have made a systematic study of such substitutions and have shown that the introduction of a third substituent into a disubstituted benzene derivative reveals for *ortho-para*-directing substituents the following diminishing series,

$$OH > NH_2 > I > Br > Cl > CH_3,$$

and similarly for the *meta*-directing substituents we obtain

$$COOH > SO_2OH > NO_2.$$

With a knowledge of these series and a knowledge of the quantitative ratio in which the isomerides are formed, when C is introduced into C_6H_5A and C_6H_5B we can usually predict with a moderate degree of accuracy the action of C on the compound C_6H_4AB.

The work of Holleman and his students has been confined largely to the first stage of substitution, in order to save experimental complications. Indeed the methods of analysis of the products of a reaction commonly used, such as freezing-point curves, solubility, etc., are subject to considerable errors since they require isolation of the mixture and some degree of purification. Chemical methods such as selective displacement of groups, sulfonation, etc., have been employed but these are limited in application.

Analysis of Mixtures of Isomers

Recently [23] a chemical method has been devised for analyzing a mixture of the three isomers of a disubstituted benzene. By this method it is possible to measure very accurately the concentration of the *meta* isomer in practically all cases in which one of the substituent groups is NH_2, OH or NO_2. This covers a majority of disubstituted benzene derivatives which are of practical importance. The method does not

[23] Francis and Hill, *J. Am. Chem. Soc.*, **46**, 2498 (1924).

distinguish between *ortho*- and *para*-compounds, but in conjunction with other methods may be used for the complete analysis of ternary mixtures. Furthermore, it may be used for the direct quantitative determination of any single isomer.

The principle of the method is that the directive influences of hydroxyl and amino compounds are so great in comparison with the directive influences of other groups that, in aqueous solution, when a hydroxyl group or an amino group is present, all available *ortho* and *para* positions are substituted quantitatively with bromine. Hence all *meta* disubstituted benzene derivatives containing the OH or NH_2 group will be tribrominated in the 2, 4 and 6 positions; *ortho* and *para* compounds, on the other hand, have one of these positions already filled, and are therefore dibrominated in the 4, 6 and 2, 6 positions respectively. One mole of a disubstituted benzene derivative would consume two moles of bromine if it consisted only of the *ortho* or *para* isomers, whereas it would consume three moles of bromine if it consisted only of the *meta* isomers. Intermediate amounts of bromine indicate mixtures of the *meta* isomer with the *ortho-para* isomers and it is evident that the percentage of the *meta* isomer can readily be obtained from the bromine consumption. In the case of nitro compounds the method involves a preliminary quantitative reduction to the corresponding amino compounds [24] by means of titanous chloride.

Bromination of Benzene Derivatives

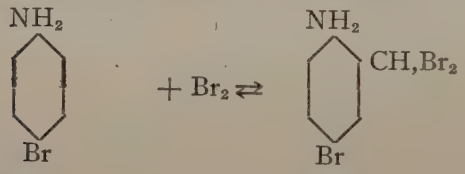
The methods described in the two foregoing paragraphs have been used in an extensive investigation [25] upon the rate of bromination, in dilute aqueous solution, of a number of related aromatic amino and phenolic compounds. This work was not confined to the first step, but when successive reactions occurred involving further bromine substitution these were studied also, because it was found that there was no simple relation between the rate of the first substitution and that of the second and third substitution.

Initial attempts to measure directly the rate of bromination by free bromine water failed because of the enormous rapidity of these reactions, aniline for example even in very dilute solution being completely brominated in a few seconds. Therefore the bromine was added in the form of a bromide-bromate mixture which slowly decomposes in acid solution liberating bromine. The observed velocity would of

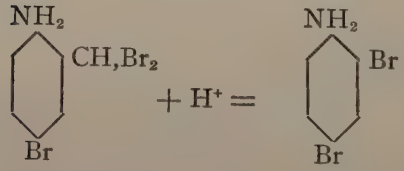
[24] Knecht and Hibbert, *Ber.*, (a) **36**, 166, 1554 (1903); (b) **40**, 3819 (1907).
[25] Francis, Hill and Johnston, *J. Am. Chem. Soc.*, **47**, 2211 (1925).

course be the comparatively slow rate of liberation of bromine from the bromide-bromate mixture and not the very rapid bromination of the aromatic amino or phenolic compound. However, by this method it is possible to get relative rates of bromination by measuring the products formed when two or more simultaneous reactions are competing for the bromine.

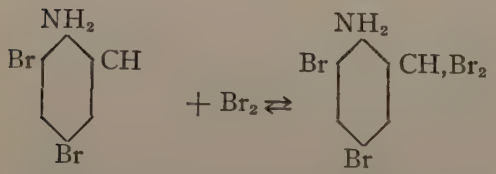
This may be illustrated by the comparatively simple example of the bromination of *p*-bromoaniline to give finally tribromoaniline. There are a number of mechanisms which might be postulated for this reaction. We might for example assume that the reaction is trimolecular, between two molecules of bromine and one molecule of *p*-bromoaniline, However the authors found that the resulting kinetic equation did not fit the observed results in any of the cases investigated, so that we have to assume that the bromination of such benzene compounds is a series of successive reactions. A possible mechanism in which the reaction is assumed to be catalytic is the following:



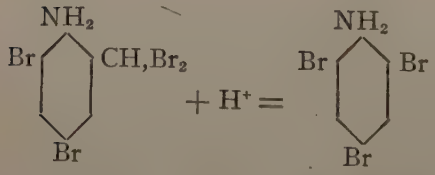
(1)



(2)



(3)



(4)

Reactions (1) and (3) are supposed to be of the instantaneous type and the concentration of the addition compound is supposed to be frac-

tionally very small; hence the rate of reaction (2) is proportional to the concentration of monobromoaniline, the concentration of bromine and the concentration of hydrogen ion. Similarly the rate of reaction (4) is proportional to the concentrations of dibromoaniline, bromine and hydrogen ion.[26] The authors show that it is possible to obtain the ratio of the velocity constants for reactions (2) and (4) by performing a series of experiments in which various quantities of bromine, as bromide-bromate mixture, are added to monobromoaniline. The quantity of bromine added in the first experiment may be perhaps 0.05 moles per mole of monobromoaniline and increases to a maximum of 2 moles of bromine, which would convert all the monobromoaniline to the tribromo derivative. In each of these experiments the bromine added goes partly to form dibromoaniline and partly to form tribromoaniline; the tribromo derivative is completely insoluble and can be estimated by filtering off and weighing.

We have therefore a series of experiments in which various known fractional amounts of bromine have been added to monobromoaniline and the amount of tribromoaniline has also been measured. A curve can be drawn showing the relation between the amount of bromine added and the fraction of the bromine converted into tribromoaniline. The shape of this curve depends on the relative velocities of the two reactions (2) and (4). This ratio may be calculated in the following manner. Suppose we start with M moles of monobromoaniline and $2M \times r$ moles of bromine, in a total volume of V liters; $2M$ moles of bromine would be required to convert M moles of monobromoaniline to tribromoaniline so that r is simply the relative fractional amount of bromine necessary for complete conversion to the tribromo derivative. Suppose that after t minutes, My moles of dibromoaniline have been formed and from this in turn Mz moles of tribromoaniline; y is the fraction of the original substance converted to dibromoaniline in t minutes and z is the fraction of the original substance converted to tribromoaniline in t minutes. The rate in reaction (2) is proportional to the concentration of monobromoaniline, the concentration of bromine and the concentration of catalyst; we have therefore,

$$\frac{\mathrm{d}\,My}{\mathrm{d}t} = K_2\left(\frac{M - My}{v}\right) \times [\mathrm{Br_2}] \times [\text{Catalyst}]. \qquad (5)$$

[26] It should be noted that we have no reasonably certain knowledge of what mechanism these reactions follow. In a later paper (Francis, *J. Am. Chem. Soc.*, **48**, 1631 (1926)), the view is adopted that the bromine atom is the active agent in such brominations.

Similarly for reaction (4), the rate is proportional to the concentration of dibromoaniline, the concentration of bromine and the concentration of catalyst; hence,

$$\frac{\mathrm{d}\,Mz}{\mathrm{d}t} = K_3\left(\frac{My - Mz}{v}\right) \times [\mathrm{Br_2}] \times [\text{Catalyst}]. \qquad (6)$$

Dividing (6) by (5) we obtain,

$$\frac{\mathrm{d}z}{\mathrm{d}y} = \frac{K_3}{K_2} \cdot \frac{y - z}{1 - y},$$

since the concentration of bromine and the concentration of catalyst is the same for each reaction. Putting $K_3/K_2 = p$ and solving we have,

$$z = C\,(1-y)^p + \frac{1 - py}{1 - p}$$

When $y = 0$, $z = 0$, hence

$$C = \frac{1}{p - 1}$$

We have then,

$$z = \frac{(1-y)^p + py - 1}{p - 1}$$

When all the bromine has been used up, we have,

$$y + z = 2r,$$

and by combination with the preceding equation we obtain,

$$(1 - 2r + z)^p + 2p(r - z) + z = 1.$$

This equation gives the desired relation between r, the bromine taken and z the tribromoaniline formed; it should therefore be possible to find by trial a value for the constant p such that the graph of this equation would correspond with the experimental curve. For the bromination of *p*-bromoaniline the curves substantially coincide when $p = 1.58$, which shows that dibromoaniline brominates at 1.58 times the rate at which *p*-bromoaniline brominates.

The curves shown in Figure 12 illustrate the variety of relationships which are obtained in these brominations. In each of the compounds three atoms of bromine enter, so that the bromination consists of three successive reactions whose relative rates determine the shape of the curve. For *m*-phenylene diamine $K_1 : K_2 : K_3$ as $1 : \infty : \infty$; consequently the compound goes at once to the tribromo derivative. For *m*-aminophenol we have $1 : 2.6 : \infty$ so that until the theoretical amount of bromine is added there will always be some monobromo derivative

and the curve will deviate from the straight line; there will be no appreciable amount of the dibromo derivative present at any time because its rate of bromination is practically instantaneous. The ratios for aniline are $1 : \infty : 1.13$ so that until the end of the experiment there will always be some dibromoaniline present; there will be no monobromoaniline present because it is brominated practically instantaneously. The ratios for phenol are $1 : 0.0035 : 0.000021$; evidently in the case of phenol each of the three stages will almost complete itself before the next stage occurs to an appreciable extent. It should be noted that the

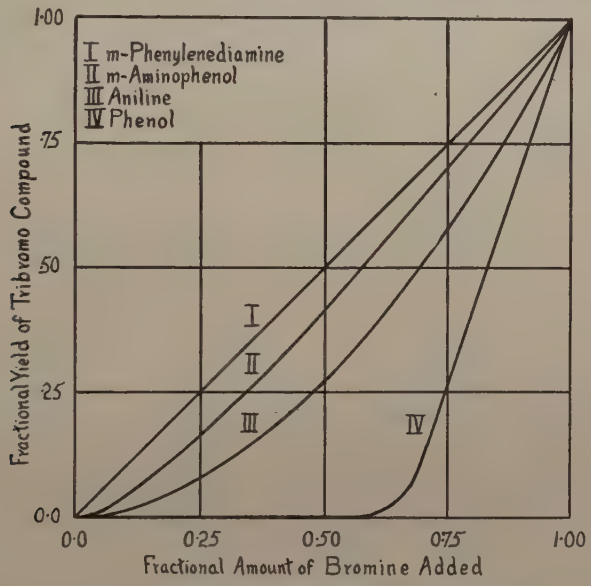


FIG. 12.—System: Benzene Derivative—Bromine.

first stage of the process really consists of three side reactions, of which the *meta* reaction may be neglected since it is very slow; the constant therefore obtained for the first stage is really a mean value for the *ortho* and *para* reactions.

It would seem that the mechanism of bromination of phenol in a non-aqueous solvent such as carbon tetrachloride has some resemblance to the action in aqueous solution. The reaction is very much slower [27] and even in excess of bromine takes several days to reach the tribromo stages; if one mole of bromine is added to one mole of phenol in car-

[27] Baines, *J. Chem. Soc.*, 121, 2810 (1922).

bon tetrachloride a theoretical yield of a mixture of *ortho*- and *para*-monobromophenol is obtained; on similar treatment with twice the quantity of bromine, a theoretical yield of 2,4-dibromophenol is obtained. Evidently the ratios $K_1:K_2:K_3$ in carbon tetrachloride have some such high value as in water. In carbon tetrachloride water appears to act as a catalyst because the rate slows up greatly on careful drying.

The calculation of the ratios $K_1:K_2:K_3$ for these more complex cases is made in a similar manner to that illustrated for monobromoaniline; fortunately the mathematical treatment is simplified because in a great many of the investigations, either two of the constants were equal or one of the reactions went with practically infinite velocity. For example aniline and with few exceptions all the *meta*-amino compounds brominate in such a way that K_2 appears to be infinite; we may suppose therefore that the first two substitutions are simultaneous but the third successive. Since neither *ortho* nor *para* bromoaniline is brominated much faster than aniline and since diethyl aniline shows a relatively slow rate of successive bromination the authors consider that $C_6H_5NBr_2$ is formed as an intermediate product in the bromination of aniline.

This work was extended in two directions (1) by making a comparison of the velocities of a large number of organic compounds and (2) by making a measure of the absolute velocities. The first part of the work consisted in making competition experiments between two organic compounds for varying amounts of bromine and from the resulting curves obtaining the relative velocity constants. The second part consisted in forming an approximate measure of the absolute velocities of some of the very slow ones and then by competition experiments passing to those far too rapid for direct measurement.

The results of these measurements [28] for 140 organic compounds are given in Table XXI, which is a valuable summary of the reactivities of organic compounds with bromine. In general the results are in accord with previous work on the order of directive influence of various constituents.

Furthermore, the directive influence of several substituents in the same ring is usually cumulative. This may be illustrated by introducing an *ortho*-methyl group into *p*-nitro aniline, which increases the velocity nearly 50 per cent, just as it does that of aniline itself. Usually the *para* position is more susceptible to attack than the *ortho*

[28] See Francis, *J. Am. Chem. Soc.*, **48**, 1631 (1926).

TABLE XXI

RELATIVE VELOCITY CONSTANTS OF BROMINATION REFERRED TO K_1-ANILINE AS UNITY

Compound	K_1	K_2	K_3
Acetanilide	0.13	....	....
Acetyl-*m*-aminophenol	16	?	?
Acetyl-*o*-toluidine	0.011	....	....
Acetyl-*p*-toluidine	.008	....	....
m-Amino-acetanilide	4 ——	—4[c]	4.5
p-Amino-acetophenone	11	21	....
m-Aminobenzoic acid	0.85—	—0.85	0.97
p-Aminobenzoic acid	6	11	.0002[b]
p-Aminobenzyl cyanide	0.3	0.6	....
m-Amino-dimethylaniline (3.5)[a]	.4	?	?
p-Amino-diphenylamine-*o*-sulfonic acid (2.6)[a]	89	?	....
m-Aminophenol	38	100 ——	—100
p-Aminophenylacetic acid	0.24	0.45	....
2-Aminotoluene-4-sulfonic acid	1.3	.3	....
2-Aminotoluene-5-sulfonic acid	2.7	.003[b]	....
4-Aminotoluene-2-sulfonic acid	0.09	.17	....
Aniline	1.00—	—1.00	1.13
Anisole (1.5)[a]	0.5	....	....
Anthranilic acid	23	5	0.0002[b]
Arsanilic acid	2.5	2	?[b]
Benzanilide	0.01	....	....
Benzene-azophenol	.22	?	?
Benzyl-aniline	15	15	15
Bromoacetanilide	0.008	....	....
3-Bromo-4-aminotoluene	.95	....	....
o-Bromoaniline	5	1.1	....
m-Bromoaniline	3 ——	—3	3.5
p-Bromoaniline	0.55	1.05	....
o-Bromophenol	.36	0.03	....
p-Bromophenol	.19	.03	....
Carbanilide (2.5)[a]	1.3	?	....
o-Chloroaniline	5	1.1	....
m-Chloroaniline	3 ——	—3	3.5
p-Chloroaniline	0.52	1	....
o-Chlorophenol	.34	0.03	....
m-Chlorophenol	5.5	.2	0.05
p-Chlorophenol	0.19	.03	....
Cinnamic acid (addition)	.03	....	....
Cinnamic aldehyde (addition)	.014	....	....
Cinnamyl alcohol (addition)	42	....	....
o-Cresol	46	.1	....
m-Cresol	100	4	0.05
p-Cresol	14	0.06	....
o-Cresotinic acid	0.6	.04[b]	....
m-Cresotinic acid	2.1	.1	?[b]
p-Cresotinic acid	0.3	.02[b]	....
2,4-Diamino-chlorobenzene	12 ——	—12	....

[a] The number of equivalents of bromine in titration when this is not indicated by the number of velocity constants.

[b] This constant is that for the displacement of a group by bromine.

[c] A tie line indicates that the substitutions so tied appear to be simultaneous.

TABLE XXI—*Continued*

Compound	K_1	K_2	K_3
2,4-Diaminotoluene	3	—3	....
2,4-Dibromoaniline	1.05	....	....
2,6-Dibromoaniline	25	....	....
2,4-Dichloroaniline	1	....	....
2,5-Dichloroaniline	20	4.5	....
3,5-Dichlorosalicylic acid	0.01[b]	....	....
Diethyl-*m*-aminophenol	4	?	?
Diethylaniline (4.5)[a]	0.13	0.02	?
2,4-Dihydroxybenzaldehyde	15	—15	0.02[b]
2,4-Dihydroxybenzoic acid	77	—77	.45[b]
Dimethylaniline (2.8)[a]	0.8	?	?
2,4-Dinitrophenol	.013	....	....
Diphenylamine (4.0)[a]	400	20	0.001
Diphenylguanidine	0.005	?	....
Diphenyl-*m*-phenylenediamine (7)[a]	3000	3000	1
Ethyl *m*-aminobenzoate	0.8	0.8	0.9
Ethyl *p*-aminobenzoate	6	11	....
Ethylaniline	0.8	0.8	0.8
Ethyl anthranilate	17	3.5	....
Ethylmetanilic acid (1.5)[a]	0.25	....	....
Ethyl salicylate	.02	?	....
Ethyl-*o*-toluidine	1.3	0.3	....
Ethyl-*p*-toluidine	0.27	.5	....
Formanilide (1.5)[a]	.06	....	....
Hydrazobenzene (2.6)[a]	13	?	....
Hydroquinone (oxidation)	15	....	....
p-Hydroxybenzaldehyde	0.09	0.002	0.001[a]
m-Hydroxybenzoic acid	.28	.03	.01
p-Hydroxybenzoic acid	.3	.03	.005[b]
p-Iodo-aniline	.24	.45	....
Metanilic acid	.52	—.52	0.6
Methylaniline	2	2	2
Methyl anthranilate	16	3.5	....
Methylanthranilic acid	19	4	....
Methyl cinnamate (addition)	0.002	....	....
Methyl salicylate	.05	.0001	....
2-Nitro-5-aminocresol-4-methyl ether	56	....	....
3-Nitro-4-aminotoluene	7	....	....
4-Nitro-2-aminotoluene	0.7	?	....
5-Nitro-2-aminotoluene	11.5	....	....
o-Nitro-aniline	25	0.04	....
m-Nitro-aniline	0.46	—.46	0.2
p-Nitro-aniline	8	.05	....
3-Nitro-*p*-cresol	0.02	....	....
m-Nitromethylaniline	.24	?	?
p-Nitromethylaniline	1.6	?	....
o-Nitrophenol	0.03	0.01	....
m-Nitrophenol	.02	.02	0.03
p-Nitrophenol	.03	.13	....
5-Nitrosalicylic acid	.0005	?[b]	....
p-Nitrosophenol	.006	.01	....
Orcinol	1000	60	—60
Orcinol monomethyl ether	200	?	?
Oxanilic acid	0.15	....	....
Phenacetin (2.7)[a]	.01	?	....

TABLE XXI—*Continued*

Compound	K_1	K_2	K_3
m-Phenetidine	12	12	14
Phenetole (1.5)[a]	0.5	....	....
Phenol	21	0.19	0.03
Phenol-3,4-disulfonic acid	0.03	.004	....
p-Phenolsulfonic acid	.17	.06	....
Phenylacetanilide	.01	....	....
m-Phenylenediamine	5.5	5.5	5.5
Phenylglycine	6	6	6
Phenylhydrazine (oxidation)	100	100	....
Phenyl salicylate	0.02	?	....
Phenylurea	4	0.1	....
Phloroglucinol	6000	500	500
Resorcinol	150	150	11
Resorcinol dimethyl ether (2.3)[a]	92	2	....
Resorcinol mono-ethyl ether	63	?	?
Resorcinol monomethyl ether	60	?	?
Rosaniline (5)[a]	2.2	?	?
Salicyl alcohol	**7**	0.06	0.002[b]
Salicyl aldehyde	0.15	.01	.0006[b]
Salicyl anilide	.09	.03	....
Salicylic acid	.4	.03	0.005[b]
Sulfanilic acid	2.6	5	.003[b]
Sulfosalicylic acid	0.07	?[b]	....
Thiocarbanilide (5)[a]	.12	?	?
Thiophenol (2.5)[a]	.11	?	?
Thymol	54	1	....
o-Toluidine	1.5	0.33	....
m-Toluidine	1.4	1.4	1.5
p-Toluidine	0.17	0.32	....
Triphenylguanidine	.002	....	....
Vanillic acid	.12	0.01[b]	....
Vanillin	.05	.00003[b]	....
Vanillyl alcohol	.02	....	....
1,2-Xylenol-4	38	2	....
1,3-Xylenol-2	35	....	....
1,3-Xylenol-4	36	....	....
1,4-Xylenol-2	52	3	....
1,2-Xylidine-4	0.18	0.34	....
1,4-Xylidine-2	2.7	1	....
m-Xylorcinol	800	....	....

position since for example the rate of substitution of the first atom of bromine in the *ortho* isomer is always greater than in the *para* isomer. A study of the table makes it evident that there are a large number of such special relationships existing for these reactions.

Other Studies of Directive Influence

A number of other studies have been made of the effect on chemical reactivity of substitution in the benzene nucleus. Franzen [29] exam-

[29] Franzen, *J. pr. Chem.*, **97**, 61 (1918). See also Franzen, Onsager and Faerden, *ibid.*, **97**, 336 (1918).

ined the effect of substitution in the ring on the rate of reduction of phenyl hydrazine and found that *ortho-para*-directing substituents in whatever position usually increase the reactivity of the hydrazine radical, whereas *meta*-directing groups usually diminish the reactivity. When substituted acetanilides are nitrated,[30] *ortho-para*-directing groups when in position 2 of acetanilide usually diminish the ease of replacement of the hydrogen atom in position 4, but may increase or diminish the ease of replacement of the hydrogen atom in position 6. In a study of the reaction [31] between the benzyl chlorides and sodium ethoxide the order *para* > *meta* > *ortho* was obtained.

Franzen and Stauble [32] have studied the bromination of β-napthylamine and have shown that the 1-, 1,6- and 1,6,3- positions are reactive, while in α-naphthol and α-naphthylamine the 2- and 4- positions seem to be equally reactive but the 5- position is unaffected. Many other similar studies have been made such as the study of the reaction between chloronitrobenzene and various substituted anilines,[33] the reaction between bromoacetophenone and a number of substituted aromatic aldehydes,[34] the benzylation of amines,[35] and the rate of reaction between ethyl iodide and the sodium salts of various substituted phenols.[36] While simple rules are evolved they are of a somewhat specialized character for each reaction and it does not seem possible as yet to draw up a set of simple rules to apply to all cases of reactions of benzene derivatives.

Sulfonation of Aromatic Compounds

A comparatively small amount of quantitative work has been done on the sulfonation and nitration of benzene and its derivatives.[37] Indeed, from the kinetic standpoint, this subject has been far less studied than such a single reaction as the inversion of cane sugar, a fact all the more surprising when we consider the technical importance as well as the scientific interest of such reactions. Of course part of the explanation of this is the complicated nature of the reactions occurring, since even in the simpler cases there are usually half a dozen

[30] Franzen and Engel, *ibid.*, **102**, 156 (1921).
[31] Franzen and Rosenberg, *ibid.*, **101**, 333 (1920).
[32] Franzen and Stauble, *ibid.*, **101**, 58 (1920); *idem, ibid.*, **103**, 352 (1921).
[33] Linke, *Ber.*, **56**, 848 (1923).
[34] Bodforss, *Z. physik. Chem.*, **102**, 40 (1922).
[35] Peacock, *J. Chem. Soc.*, **127**, 2177 (1925); *idem, J. Phys. Chem.*, **30**, 673 (1926).
[36] Goldsworthy, *J. Chem. Soc.*, **129**, 1254 (1926).
[37] For earlier work see Bamberger, *Ber.*, **28**, 401 (1895); *idem, ibid.*, **30**, 654, 1281, 2274 (1897); Baumann, *ibid.*, **9**, 55, 1715 (1876); *idem, ibid.*, **11**, 1907 (1878).

side reactions and successive reactions occurring; usually too, the benzene ring itself is broken down to a slight extent making quantitative study still more difficult.

When benzene is dissolved in sulfuric acid, benzene monosulfonic acid is formed, and at higher temperatures and on standing this reacts with more sulfuric acid to give diphenyl sulfone, $(C_6H_5)_2SO_2$. The sulfonation of benzene does not go to completion, but reaches an equilibrium when the ratio $\frac{H_2SO_4}{H_2SO_4 + H_2O} = 0.78$. The published work on this reaction has been concerned mainly with the technical preparation of the substance, such as its preparation by passing benzene vapor into the acid [38] or the sulfonation in the liquid state and removal of the sulfonic acid by extraction with benzene.[39] It would be interesting to know to what extent this reaction is catalytic, and whether the presence of water greatly affects the rate as in so many reactions involving sulfuric acid. That the reaction is affected by catalysts is indicated by a claim [40] that a trace of iodine increases the yield of sulfonic acid in the sulfonation of aromatic compounds. Naphthalene is converted into naphthalene-β-monosulfonic acid by sulfuric acid and at higher temperatures the 2, 7-disulfonic acid is formed. Beyond the fact that the water diminishes the rate of the reaction [41] practically nothing is known of the kinetics of the reaction.

A similar paucity of information exists with regard to the sulfonation of other aromatic compounds. Thus Campbell [42] in a study of the rate of sulfonation of phenols states: "The author has been unable to trace any record in the literature of work showing the comparative difference in the velocity constant of the sulfonation of phenols under varying conditions. In this paper the effect of temperature and the methyl group is described." It is interesting that the sulfonation of the three cresols follows exactly the same order as the bromination experiments in Table XXI; under certain definite conditions of reaction *meta*-cresol is preferentially and far more readily sulfonated than either *ortho*- or *para*-cresol. As is usual in sulfonating reactions, the relative rates depend largely on the temperature. At 20° the order of sulfonation in diminishing series is, *meta*-cresol, phenol, *ortho*-cresol,

[38] Tyrer, U. S. Patent No., 1,210,725; Harvey and Stegeman, *J. Ind. Eng. Chem.*, **16**, 842 (1924).
[39] Peterkin, *ibid.*, **10**, 738 (1918).
[40] Heinemann, *J. Soc. Ind. Chem.*, **35**, 1008 (1916).
[41] Ambler, Lynch and Haller, *J. Ind. Eng. Chem.*, **16**, 1264 (1924).
[42] Campbell, *J. Chem. Soc.*, **121**, 847 (1922).

and *para*-cresol, but above 65° the *meta*-cresol and phenol interchange places. Under the conditions of the experiment only monosulfonic acids were formed.

Nitration of Aromatic Hydrocarbons

The literature dealing with the kinetics of the nitration of benzene derivatives is also extremely meagre although in the past few years the subject has been studied to some extent from the quantitative standpoint. Benzene is readily nitrated to the first and second stages but the third stage occurs only with great difficulty. A recent study showed that nitration gave the well-known 1,3,5-isomer, (melting point 121°), but occasionally a trinitrobenzene of 61° melting point was obtained.[43] This appears to be a new form of the 1,3,5-compound but it appeared in an erratic manner and the experiments failed to establish the conditions under which it was formed. This behavior caused the authors to suspect catalysis by traces of some accidental impurity but they were unable to find anything which would affect the course of the reaction.

The products formed in the nitration of toluene and their relative amount at various temperatures have recently been carefully studied.[44] Various experiments were conducted in which the toluene was nitrated both with and without the addition of sulfuric acid. Neither the composition nor the temperature has any appreciable effect on the proportions of the different isomers, the results showing that mononitrotoluene obtained by the nitration of toluene contains 61.5 to 62.5 per cent *ortho-*, 33.5 to 32 per cent *para-* and 4.5 to 4.2 per cent *meta*-nitrotoluene. By nitrating this mixture to the further stages the following results are obtained:

Dinitrotoluenes		Trinitrotoluenes	
Isomer	Per Cent	Isomer	Per Cent
2:4	74.8	2:4:6	95.5
2:6	20.7	3:4:6	2.9
3:4	2.5	2:3:4	1.3
2:3	1.1	2:3:6	0.3
2:5	0.9		

From these results a rough idea of the relative velocity constants may be obtained.

[43] Radcliffe and Pollitt, *J. Soc. Chem. Ind.*, **40**, 45T (1921). Note, however, that these results have been questioned by Gibson, *ibid.*, **40**, 90T (1921).
[44] Gibson, Duckham and Fairbairn, *J. Chem. Soc.*, **121**, 270 (1922).

The only comprehensive study of the effects of catalysts in nitration seems to have been made in some recent studies [45] on the use of mercuric nitrate in the nitration of aromatic substances. When benzene is warmed with 60 per cent nitric acid containing mercuric nitrate in solution, mononitrobenzene and picric acid are produced in approximately equal amounts. The mechanism of this reaction is of considerable interest, but the most plausible hypothesis, that nitrobenzene is first formed which is oxidized to *o*-nitrophenol under the catalytic influence of the mercury salt, followed by the third stage of nitration to picric acid, is not correct. For example none of the nitrobenzenes yield picric acid when treated with nitric acid so that the presence of mercuric nitrate does not encourage the oxidation of the hydrogen atoms of a nitrated aromatic nucleus; this is all the more curious since the hydrogen atoms of symmetrical trinitrobenzene are so active that a lukewarm aqueous solution of potassium ferricyanide oxidizes the substance to picric acid. Dilute nitric acid of about 10 per cent strength boiled with benzene in the presence of mercuric nitrate produces considerable 2,4-dinitrophenol, while it yields scarcely enough nitrobenzene to be detected by its odor. Nitration of toluene and chlorobenzene using mercury as catalyst gave trinitro-*m*-cresol and trinitro-*m*-chlorophenol respectively.

The authors conclude that the surprising formation of *meta*-substituted hydroxyl compounds from toluene and chlorobenzene indicate that the hydroxyl group and at least one nitro group are probably introduced simultaneously and that the course of the reaction involves the intermediate formation of a complex molecular compound. The formation of *meta*-substituted compounds and the fact that mercury appears to be unique among metals in this type of catalysis indicates that the phenomenon is related to mercuration processes.[46] The reaction may be best explained by supposing that the first step involves the addition of mercuric nitrate to adjacent carbon atoms of the benzene nucleus, the $—NO_2$ group adding to one and the residue $—OHgONO_2$ adding to the other. The hydrogen atoms originally resident on the carbon atoms to which the mercuric nitrate has added are now supposed to be removed by oxidation.

Naphthalene nitrates very easily to the nitro derivatives so that to

[45] Davies, Worrall, Drake, Helmkamp and Young, *J. Am. Chem. Soc.*, **43**, 594 (1921); Davies, *ibid.*, **44**, 1588 (1922). See also Blechta, *Chem. Listy* **14**, 161 (1920); Procházka, *ibid.*, **15**, 59 (1921).

[46] Coffey, *J. Chem. Soc.*, **127**, 1029 (1925); Burton, Hammond and Kenner, *ibid.*, **129**, 1802 (1926).

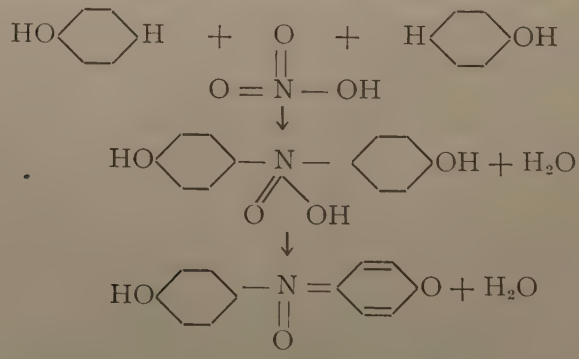
obtain nitronaphthole directly from naphthalene weak acid and low temperature must be used; the yields obtained are comparatively small, however.

Recently it has been reported [47] that a 45 to 50 per cent solution of nitrosulfonic acid in fuming nitric acid is a better nitrating agent than the usual mixture of nitric and sulfuric acids. A trace of iodine apparently catalyzes the formation of certain dinitro derivatives.

Nitration of Phenol

The nitration of phenol and its derivatives has been more extensively studied than other aromatic substances, and some quantitative kinetic measurements are available. In this connection we may consider briefly a study of the stability of phenol and its derivatives to aqueous potassium permanganate.[48] In general, phenol and its mononitro- and carboxy-derivatives are extraordinarily unstable towards potassium permanganate, but the more heavily substituted compounds are comparatively stable. With the more complicated compounds a kinetic study gave a fairly good bimolecular constant, indicating that the first stage, namely, that involving the rupture of the ring, proceeds more slowly than the subsequent reactions. This instability of the ring leads to considerable oxidation in nitration,[49] depending on the process used. We may note that substitution of the hydrogen atoms of phenol renders it more stable to oxidizing action by nitric acid; thus Hammick [50] has shown that trinitrophenol is oxidized only extremely slowly by the mixed acid used to nitrate phenol.

In addition to oxidation we may have under certain conditions a coupling process taking place [51] which may be represented as follows:



[47] Varma and Kulkarni, *J. Am. Chem. Soc.*, **47**, 143 (1925).
[48] Hinshelwood, *J. Chem. Soc.*, 115, 1180 (1919).
[49] Rice, *J. Am. Chem. Soc.*, **42**, 2665 (1920).
[50] Hammick, *J. Soc. Chem. Ind.*, **40**, 26T (1921).
[51] Meyer and Elbers, *Ber.*, **54**, 337 (1921).

The indophenol-N-oxide is prepared by adding concentrated nitric acid to a solution of phenol in glacial acetic and sulfuric acids. Kinetic measurements showed the reaction to be trimolecular so that the compound is formed directly from two moles of phenol and one mole of nitric acid.

The kinetics of the nitration of phenol and its derivatives has been studied by Klemenc and his co-workers.[52] They find that nitration in presence of sulfuric acid gives excellent constants for bimolecular reactions, the constants not being affected by nitrous acids or lower oxides of nitrogen. This is in marked contrast to the behavior in ethereal solution in which nitration proceeds only in presence of oxides of nitrogen in which nitrogen has a valency lower than five. The nitration is always accompanied by oxidation and is therefore catalytic. The authors find that the velocity of nitration is proportional to the 2.5 power of the concentration and they assume that the actual nitrating agent is an intermediate compound, $2\ HNO_3,NO_2$. However, except in sulfuric acid solution the course of the reaction is by no means clear.

The preparation of picric acid from phenol by the successive action of sulfuric and nitric acids has been investigated with considerable care although only a small amount of work has been done from the kinetic standpoint. It seems clear from studies of this reaction [53] as well as from Hinshelwood's experiments on the stability of phenols towards permanganate, that the effect of the sulfonation is to diminish the velocity of undesirable side reactions leading to rupture of the ring and formation of oxalic acid. Olsen and Goldstein however disagree with this view.[54] "It is frequently stated that this is done because the sulfonic acid groups "protect" the phenol from the oxidizing action of the nitric acid. What actually occurs is that the rate of the nitrating action is so much reduced by the presence of one or more negative or acidic sulfonic acid radicals that the nitration can proceed smoothly, and the large quantity of heat liberated by the reaction can escape without causing an excessive rise in temperature with its attendant acceleration of the reaction and hence still higher temperatures."

[52] Klemenc, *Monatsh.*, **35**, 85 (1914); Klemenc and Ekl, *ibid.*, **39**, 641 (1918); Klemenc and Schöller, *Z. anorg. Chem.*, **141**, 231 (1924).

[53] See Marqueyrol, Carré and Loriette, *Bull. Soc. chim.*, **27**, 143 (1920); King, *J. Chem. Soc.*, **119**, 2105 (1921).

[54] Olsen and Goldstein, *J. Ind. Eng. Chem.*, **16**, 66 (1924).

Nitration of Other Aromatic Compounds

King has made a careful study of the nitration of the various phenol sulfonic acids and concludes that in concentrated sulfuric acid the hydrogen of the nucleus tends to be replaced by the nitro-group, whereas in dilute sulfuric acid nitrolysis occurs and the sulfo-groups are replaced by the nitro-group. In dilute solution nitric acid exerts an oxidizing action, resulting in the formation of oxalic acid; this is the more marked as the phenol nucleus is less protected by substituents.

The nitration of halogenated phenols has also been studied but only in a qualitative manner.[55] Sometimes the bromine atoms in a bromophenol are replaced by NO_2 groups. Certain *para*-halogen substituted phenols behave peculiarly on nitration, in that the halogen atom is replaced by the nitro-group and migrates to the *ortho* position.

The sulfonation and nitration of aromatic substances appear to be nearly all slow reactions which can be studied from the kinetic point of view. It seems very desirable to make such studies in order to make clear the mechanism of these reactions and to determine if catalytic influences play a part in determining the reaction rates. A review of the literature shows that many of these reactions behave somewhat like the nitration of bromo-*m*-cresol derivatives, commented on by Gibbs and Robertson as follows: "The conditions which determine the formation of one or other of these compounds are very subtle, seeming to depend on the rate of addition of the nitric acid, its quantity, the state of dilution and the temperature."

Other studies of nitration processes have been made by Hoeflake [56] on the nitration of phenol derivatives, by Marshall [57] on the manufacture of hexanitrodiphenylamine, by Nolan and Chapman [58] on the formation of tetryl, and by Chattaway and Coulson [59] on the nitration of benzil; most of these researches are qualitative in character.

[55] Gibbs and Robertson, *J. Chem. Soc.*, **105**, 1885 (1914); Raiford, *J. Am. Chem. Soc.*, **44**, 158 (1922).
[56] Hoeflake, *Rec. trav. chim.*, **36**, 24 (1916).
[57] Marshall, *J. Ind. Eng. Chem.*, **12**, 336 (1920).
[58] Nolan and Chapman, *Sci. Proc. Roy. Dublin Soc.*, **17**, 219 (1923).
[59] Chattaway and Coulson, *J. Chem. Soc.*, **129**, 1070 (1926).

Chapter IX.

General Reactions.

In this chapter some of the more important of a great number of general reactions are described from the physical-chemical standpoint. A considerable number of physical-chemical studies have been made on these reactions and it is gratifying to find that such studies have been very effective in elucidating the reaction mechanism.

Friedel and Crafts Reaction

Friedel and Crafts [1] in a study of the action of aluminium and its salts on organic substances, discovered the remarkable condensing powers of the aluminium halides. They investigated the condensation of alkyl halides and aromatic hydrocarbons in presence of aluminium chloride and also the effect of this salt on complex hydrocarbons. Further work has shown that aluminium chloride may be put to the most diverse applications and consequently the reaction has been used very extensively. Each year adds, not merely to the list of syntheses, but also to the types of reactions that can be brought about by its means. Consequently the mechanism through which this and similar catalysts act is of the greatest interest.

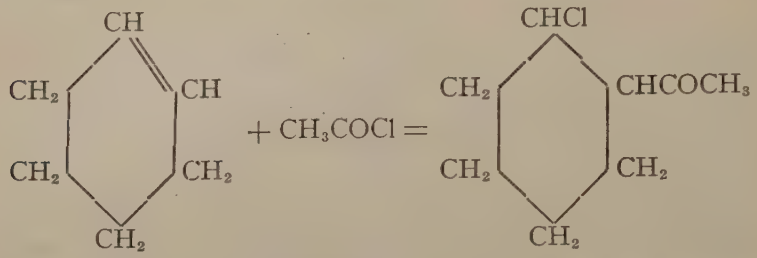
The isolation of addition compounds of aluminium chloride and acid chlorides or acid anhydrides led to the general belief that the formation of such additive compounds was a necessary step in the Friedel-Crafts reaction. The halogen compound (or the acid anhydride) is supposed to become active in this addition compound, and hence able to condense with the hydrocarbon. Böeseken [2] has put forward the view that the reactions take place according to the following scheme:

$$RCOCl + AlCl_3 = RCOCl,AlCl_3$$
$$RCOCl,AlCl_3 + R'H = RCOR',AlCl_3 + HCl$$
$$RCOR',AlCl_3 + xH_2O = RCOR' + AlCl_3 + xH_2O$$

[1] Friedel and Crafts, *Ann., de Chim.*, [6] **1**, 449 (1884).

[2] Böeseken, *Rec. trav. chim.*, (a) **19**, 19 (1900); (b) **20**, 102 (1901); (c) **22**, 301 (1903); (d) **23**, 98 (1904); (e) **24**, 6 (1905); (f) **30**, 148, 381 (1911); (g) **31**, 367 (1912); (h) **32**, 1 (1913); see also Perrier, *Ber.*, **33**, 815 (1900); Böeseken and Bastet, *Rec. trav. chim.*, **32**, 184 (1913).

Darzens [3] studied the reaction between acetyl chloride and tetrahydrobenzene, and concluded that the primary reaction is addition at the double bond:



The chloroketone forms a stable complex compound with the aluminium chloride catalyst. Darzens made a study of this reaction using other metallic chlorides as catalysts. Those without action are the chlorides of sulfur, copper, mercury, tin (divalent); on the other hand the chlorides of boron, iron and antimony catalyzed the reaction but gave poorer yields than aluminium chloride; titanium tetrachloride gave very satisfactory yields.

Before discussing the mechanism of the Friedel-Crafts reaction in greater detail it seems desirable to point out that there are two main lines of attack on the problem, namely an investigation of double compound formation, and an investigation of the kinetics of some of the reactions which occur at convenient speeds. Double compounds between aluminium chloride and organic compounds have been comparatively slightly investigated in spite of the large amount of work that has been done to elucidate the mechanism of the Friedel-Crafts reaction. There is considerable doubt as to whether some of the compounds described in the literature have any real existence. An example typical of many describes a compound as a yellow oil, insoluble in carbon disulfide, consisting of two or three components present in approximately simple stoichiometric ratios. Without further characterization it is of course very doubtful whether any compound is present at all in the mixture since the aluminium chloride may be merely "salting out" the components from an excess of the solvent. Even when a well defined crystalline compound with a definite melting point can be isolated we have no means of judging how firmly the two components are joined together.

While it is undoubted that aluminium chloride combines extensively

[3] Darzens, *Compt. rend.*, **150**, 707 (1910); see also Wieland and Bettag, *Ber.*, **55**, 2246 (1922).

with a great variety of organic compounds only a few investigations have been made in which freezing-point composition diagrams have been obtained which would enable us to judge in a semi-quantitative manner the relative extent of combination of the components. If we confine ourselves to such investigations (*see* p. 56) we find that hydrocarbons cannot combine extensively with aluminium chloride for they do not yield isolable compounds, acid chlorides show fairly extensive combination and yield isolable compounds, and nitro compounds combine extensively and in the case of the simpler derivatives yield not only 1 : 1 compounds but also 1 : 2 compounds. It would seem very desirable to extend these investigations and especially to conduct them in connection with kinetic studies of the reaction so that we would have information as to the relative extent of combination between the aluminium chloride and the reactants, products and solvent.

Olivier [4] has conducted several extensive kinetic studies of the reaction between acid chlorides and benzene in different solvents. Thus *p*-bromobenzenesulfonyl chloride reacts with measurable velocity and has the additional advantage that it is not decomposed when the reaction mixture is diluted with water to remove aluminium chloride. Owing to several factors such as the presence of simultaneous reactions, the complicated nature of the reaction itself, and the difficulty of devising a satisfactory analytical procedure, it is not easy to draw conclusions free from all doubt. However Olivier brings forward considerable evidence in favor of the view that the organic acid chloride reacts only in the form of a 1 :1 compound with aluminium chloride and that the rate is proportional to the concentration of this complex, so that we have, for *p*-bromobenzenesulfonyl chloride,

$$C_6H_4BrSO_2Cl,AlCl_3 + C_6H_6 = C_6H_4BrSO_2,AlCl_2 + C_6H_5Cl + HCl.$$

This mechanism explains the fact that in a large number of reactions one molecule of aluminium chloride per molecule of reactant is necessary for good yields.[5] It should be noted also that a slight excess of aluminium chloride over the amount required to form the 1 :1 double compound causes a great increase in velocity, which suggests that the benzene requires activation as well as the organic acid chloride. If we assume therefore that the ternary compound $C_6H_4BrSO_2Cl,AlCl_3,C_6H_6$ is formed at a measurable rate and has only a fugitive existence, the mechanisms of Olivier and Böeseken become very similar.

[4] Olivier, *Rec. trav. chim.*, **33**, 91 (1914); *idem, ibid.*, **35**, 109, 166 (1915); *idem, ibid.*, **37**, 205 (1918). See also Steele, *J. Chem. Soc.*, **83**, 1470 (1903).

[5] See Rubidge and Qua, *J. Am. Chem. Soc.*, **36**, 732 (1914).

A puzzling feature of the reaction is an autocatalytic effect that is not due entirely to the hydrochloric acid liberated during the reaction, although this very probably contributes towards a greater rate of reaction. The effect seems to be due to the production of traces of sulfur chlorides, formed from the carbon disulfide solvent, which catalyze the reaction to form *p*-bromobenzenesulfonic acid instead of the sulfone. This obscure catalytic effect of traces of substances in the Friedel-Crafts reaction has been noted in other reactions also. Thus pyridine derivatives and benzoyl chloride in presence of aluminium chloride do not yield ketones when absolutely pure;[6] if however a trace of thionyl chloride is added, the reaction proceeds readily along normal lines and good yields of ketones are produced. A similar effect was found when aromatic hydrocarbons and pyridine carboxylic acid chlorides were used. The elimination of hydrogen from aromatic nuclei[7] and the union of the residues under the catalytic influence of aluminium chloride also suggests the possibility of a trace of some other catalyst since these reactions are very capricious in their behavior. It seems significant also that nitrobenzene is used as a solvent for all these reactions, as it appears to exercise some specific influence which is perhaps connected with the extensive compound formation between it and aluminium chloride.

The quantity of aluminium chloride required in order to bring about condensations varies very greatly with the constitution of the reacting substances. In some cases traces are sufficient, while in others a molecular proportion of the catalyst is required. When acid anhydrides are used,[8] two or more molecular proportions of aluminium chloride are necessary in order to obtain good yields. Doubtless the extent of combination between the products of the reaction and the aluminium chloride partly determines the amount required, but it does not seem possible to settle this question until more information is available regarding the extent of compound formation between aluminium chloride and organic compounds.

The catalytic influence of other metallic chlorides has been investigated[9] by preparaing benzophenone from benzoyl chloride and benzene using the different catalysts under identical conditions. The re-

[6] Wolffenstein and Hartinch, *Ber.*, **48**, 2043 (1915).
[7] School and Nuemann, *Ber.*, **55**, 330 (1922).
[8] See Noller and Adams, *J. Am. Chem. Soc.*, **46**, 1889 (1924).
[9] Gangloff and Henderson, *J. Am. Chem. Soc.*, **39**, 1420 (1917).

sults indicated that aluminium chloride was best, as is shown by the following list, the yields obtained being given in brackets:

$AlCl_3$ (70%), $FeCl_3$ (60%), $ZnCl_2$ (30%), $CrCl_3$ (0%), Cu_2Cl_2 (0%).

Menschutkin [10] carried out a similar research using benzoyl chloride and *m*-xylene. He found that the chlorides or bromides of calcium, strontium, barium, cadmium and magnesium had a negligibly slight influence; mercury and zinc salts, particularly the latter, catalyze the reaction but require a much higher temperature than aluminium chloride. In these reactions also there is an incubation period during which a black resinous substance is formed which seems to be the actual catalyst; the mechanism is therefore heterogeneous and probably quite different from the ordinary Friedel-Crafts reaction in which aluminium chloride is used. Further work using antimony trichloride and tribromide [11] showed that these are good catalysts for the reaction, though inferior to aluminium chloride.

Kinetic measurements were made of the rate of the reaction between benzoyl chloride and benzene and its homologs. The rate is proportional to the concentration of benzoyl chloride and to the concentration of the hydrocarbon but is proportional to the square of the concentration of the antimony halide. It is significant that antimony halides form 2:1 compounds with benzene and its homologs (p. 59), so Menschutkin postulates the first stage as consisting of a very rapid reaction to form a compound of antimony trichloride with the hydrocarbon, 2 $SbCl_3,C_6H_5R$; this then reacts at a measurable rate with the benzoyl chloride to form a compound of antimony trichloride with the ketone, $SbCl_3,C_6H_5COC_6H_4R$, hydrochloric acid being eliminated; the double compound decomposes at the temperature of the experiment, regenerating the antimony trichloride catalyst. The relative velocity constants of benzene, toluene, *p*-, *o*-, and *m*-xylene are 1, 12, 21, 32 and 80 respectively, which illustrates the general behavior that substituting the hydrogen atoms in benzene by alkyl radicals markedly increases the rate of reaction.

It seems evident from the kinetic studies made, that the mechanism of the Friedel-Crafts reaction is dependent on the catalyst used, being quite different with different catalysts. However a study of the rate of chlorination of nitrobenzene [12] using aluminium chloride and stannic

[10] Menschutkin, *J. Russ. Chem. Soc.*, **47**, 1853 (1915) (*C.A.* **10**, 1339 (1916)).
[11] *Idem, ibid.*, **45**, 1710 (1913); *idem, ibid.*, **46**, 259 (1914).
[12] Goldschmidt and Halfdon, *Z. physik. Chem.*, **48**, 424 (1904).

chloride as catalysts showed that in each case the rate is proportional to the concentration of the catalyst and in each case the temperature coefficient $k_{t+10}/k_t = 1.3$ approximately. The catalytic influence of the chlorides of iron, aluminium and tin diminish in the order given and the chlorides of antimony, phosphorus and arsenic exert practically no catalytic influence.

The authors also studied the reaction of benzyl chloride and anisole using aluminium chloride as catalyst and found the rate to be proportional to the concentration of catalyst. The rate is nearly doubled for a rise in temperature of 10°.

Acetal Formation

Aldehydes react to give polymers, esters, adols or benzoins depending primarily upon the condensing agent employed and to a less extent upon the specific aldehyde involved. The condensation of an aldehyde with an alcohol to give an acetal [13] is brought about by a number of catalysts. The products of the reaction,

$$CH_3CHO + 2\,C_2H_5OH \rightleftarrows CH_3CH(OC_2H_5)_2 + H_2O$$

are in equilibrium when the reaction has proceeded about three quarters to the right. Fischer and Giebe found that a 1 per cent solution of anhydrous hydrogen chloride in alcohol brought about the condensation giving a yield of about 50 per cent. Adkins and Nissen used calcium chloride as a catalyst for the reaction and obtained a 75 per cent yield; calcium chloride, calcium nitrate and lithium chloride were found to be the best catalysts and to be about equally efficient. Many other salts were tried and the surprising observation was noted that sodium chloride does not catalyze the reaction. The authors regard the reaction as involving a true example of catalysis. The salt used cannot be merely a dehydrating agent because such good dehydrating agents as zinc chloride and calcium bromide are only poor catalysts. Adkins and Nissen conclude that "the data in this paper are inadequate for any proper interpretation of the mechanism of the action of the salt in the condensation of the alcohol and the aldehyde," and that further investigation upon the condensations of aldehydes is necessary to interpret the mechanism of these reactions.

The study was continued by Adams and Adkins, who prepared a large number of acetals and investigated the relative efficiencies of fer-

[13] Fischer and Giebe, *Ber.*, (a) **30**, 3053 (1897); (b) **31**, 545 (1898); Adkins and Nissen, *J. Am. Chem. Soc.*, **44**, 2749 (1922); Adams and Adkins, *ibid.*, **47**, 1358, 1368 (1925); Reichert, Bailey and Nieuwland, *ibid.*, **45**, 1552 (1923).

ric chloride, calcium chloride and hydrogen chloride as catalysts. Ferric chloride is a very much better catalyst for the production of methylal from paraformaldehyde, while calcium chloride is far superior for the production of acetal. The authors showed that the equilibrium point is independent of the catalyst providing the solution is kept homogeneous. They also noted that there is a close correlation between the ability of a salt to form an alcoholate and its ability to catalyze acetal formation. All known catalysts for the acetal reaction give an acidic solution when dissolved in water; the addition of a very small amount of an alkali such as sodium carbonate greatly decreases the catalytic power of calcium chloride. The authors consider the possibility that the real catalyst for the acetal reaction is the hydrogen ion but conclude that the evidence is against this view and that the seat of catalytic activity is probably at the anion end of the undissociated salt or acid, although the efficiency of this portion of the molecule is profoundly modified by the element at the other end of the molecule.

It is interesting to note that Reichert, Bailey and Nieuwland have found that acetals may be prepared from acetylene and an alcohol in presence of a mercury salt:

$$C_2H_2 + 2ROH = CH_3CH(OR)_2.$$

Since dry acetylene gas reacts with anhydrous alcohols in presence of concentrated sulfuric acid and a mercury salt to form the acetals, we must assume that acetaldehyde is not an intermediate product of the reaction.

Condensation of Aldehydes to Esters

While aluminium chloride is a good catalyst for the condensation of aldehydes to acetals, another salt of aluminium, the ethoxide, catalyzes the condensation of aldehydes to esters,

$$2\,RCHO = RCOOCH_2R,$$

a reaction first discovered by Tischtschenko.[14] Magnesium chloride also catalyzes the reaction. Child and Adkins [14] showed that aluminium ethoxide exists in two allotropic forms which do not differ in their catalytic activity if the difference in their solubility is taken into consideration. Aluminium isopropoxide and butoxide are much better catalysts than the ethoxide. Zinc, mercuric and aluminium chlorides

[14] Tischtschenko, *J. Russ. Phys. Chem. Soc.*, **38**, 355, 482 (1906); Henle, *Ber.*, **53**, 719 (1920); Child and Adkins, *J. Am. Chem. Soc.*, **45**, 3013 (1923); *idem, ibid.*, **47**, 798 (1925).

are promoters for the reaction whereas alcoholic substances are inhibitors.

Several experiments were performed to discover whether the reaction was taking place in a homogeneous or heterogeneous system. Observations with the ultramicroscope showed no evidence of a colloidal solution and the rate of reaction was no greater in experiments in which solid ethoxide was kept in the reaction flask. The authors find that the rate of this reaction is comparatively slightly affected by considerable changes in concentration of catalyst and aldehyde and conclude that complex compound formation may explain the result: "it appears that the speed of formation of some sort of an aldehyde-catalyst complex is very rapid, while the speed of its decomposition into ester and alkoxide is slow. Anything, therefore, that will hasten this decomposition should hasten the ester condensation, while anything that retards the decomposition should retard the reaction, even though there be an excess of active catalyst present." This explanation however leaves untouched the main difficulty, namely, that the rate of the reaction should be proportional to the concentration of the aldehyde-catalyst complex, which in turn should depend on the concentrations of the two components. These reactions appear to go to completion or until the catalyst becomes inactive due to precipitation by water or the retarding effect of the other by-products of the reaction. An additional point of interest in this formation of esters from aldehydes is that the reaction has a negative temperature coefficient.

Other Reactions of Aldehydes

Meerwein and Schmidt [15] have worked out a practical method for reducing aldehydes to alcohols by treating an aldehyde with about 30 per cent of its weight of aluminium ethoxide in absolute alcohol. The course of the reaction may be represented as follows:

$$RCHO + Al(OC_2H_5)_3 \rightleftarrows RCH(OAl(OC_2H_5)_2)OC_2H_5,$$
$$RCH(OAl(OC_2H_5)_2)OC_2H_5 = RCH_2OAl(OC_2H_5)_2 + CH_3CHO.$$

Since the acetaldehyde may react with the aluminium ethoxide, it is removed by a current of nitrogen or by distillation.

Verlay [15] has studied the action of aluminium ethoxide on aldehydes in presence of an excess of alcohol and finds that the principal reaction is an exchange of groups as represented by the following equation:

$$RCHO + CH_3CH_2OH = RCH_2OH + CH_3CHO.$$

[15] Meerwein and Schmidt, *Ann.*, **444**, 221 (1925); Verlay, *Bull. Soc. chim.*, **37**, 537 (1925).

The Tischtschenko change to form an ester occurs only as a secondary reaction.

It seems probable that the best way to regard these reactions is to assume that the reactants are held together by secondary valence forces through the aluminium ethoxide and that the reaction then occurs. In the present state of our knowledge more than this can hardly be said with any degree of certainty. It may be noted that Child and Adkins found that solvents decreased the rate of condensation of aldehydes to esters when catalyzed by aluminium ethoxide; also that aluminium chloride, ferric chloride, zinc chloride and mercuric chloride react with aluminium ethoxide to give complexes which are very much more active for the ester condensation than is aluminium ethoxide itself.

Recently Adams and Vollweiler [16] studied the addition of acid halides and aldehydes and gave a brief review of previous work. The action is represented by the following equation for benzoyl bromide and benzaldehyde;

$$C_6H_5COBr + C_6H_5CHO = C_6H_5CHBrOCOC_6H_5.$$

We thus get direct addition to form halogen-substituted esters. The substances are made merely by bringing equal molecular weights of the aldehyde and acid halide together and allowing the mixture to stand in a well stoppered flask until solidification takes place. Various aromatic aldehydes were condensed with many aromatic acid chlorides and bromides and oxalyl bromide. The individual compounds differ greatly among themselves in the ease of formation. Thus benzoyl bromide and benzaldehyde react to give a solid product in the course of a day or two, while benzoyl bromide and acetovanillin evolve much heat and solidify in a few hours. The nitrobenzoyl chlorides give solid products after standing together for about a week.

The kinetics of these reactions and the equilibrium condition have not yet been worked out. It would be interesting to know the equilibrium point when the system is kept homogeneous and also to know if the rate is determined by the concentration of both reactants and if it is susceptible to catalytic influence.

Meerwein [17] has investigated an extremely interesting condensation of an aldehyde or ketone with an unsaturated aldehyde, the action being represented by the following equation:

$$C_6H_5CH_2CHO + RCH:CHCHO = CHOCH(C_6H_5)\,CHRCH_2CHO.$$

[16] Adams and Vollweiler, *J. Am. Chem. Soc.*, **40**, 1732 (1918). See also French and Adams, *ibid.*, **43**, 651 (1921); Ulich and Adams, *ibid.*, **43**, 660 (1921).

[17] Meerwein, *J. pr. Chem.*, **97**, 225 (1918).

The reaction has been investigated only qualitatively from the preparative point of view and occurs in methanol solution in presence of an alkaline catalyst such as sodium methoxide, pyridine or diethylamine.

Cannizzaro's Reaction

When benzaldehyde is shaken with an excess of a strong solution of sodium hydroxide, Cannizzaro's reaction occurs, the reaction mass containing equal molecular equivalents of sodium benzoate and benzyl alcohol and little or no unchanged benzaldehyde:[18]

$$2\,C_6H_5CHO + NaOH = C_6H_5COONa + C_6H_5CH_2OH.$$

Further study of the reaction showed that these products result from the hydrolysis of benzyl benzoate, which is formed as an intermediate product. The reaction may even be carried out in aqueous sodium hydroxide solution, and if the solution be cooled considerable quantities of benzyl benzoate are obtained. In a study of this reaction Lachman [18] considered the addition of benzoyl bromide to benzaldehyde which unite slowly to form bromobenzyl benzoate.[19]

$$C_6H_5COBr + C_6H_5CHO = C_6H_5CO - O - CHBrC_6H_5.$$

He showed that the addition product is a compound with an oxygen linking as indicated by its formula and that it is not a substance such as benzil hydrobromide, $C_6H_5COCBr(OH)C_6H_5$, in which the central carbon atoms are directly united. Lachman however does not favor the hypothesis that in Cannizzaro's reaction two molecules of benzaldehyde unite directly under the influence of hydroxyl ion to give benzoyl benzoate,

$$C_6H_5CHO + C_6H_5CHO = C_6H_5CO - O - CH_2C_6H_5.$$

He prefers to assume that the benzyl benzoate represents the last stage of the following mechanism: compounds containing the carboxyl group readily add sodium hydroxide (or alkoxide) and these addition products show strongly additive properties toward other carbonyl compounds. We have therefore,

$$C_6H_5CH(OH)ONa + C_6H_5CHO = C_6H_5CH(OH) - O - CH(ONa)C_6H_5.$$

[18] Cannizzaro, *Ann.*, **88**, 129 (1853); Claisen, *Ber.*, **20**, 646 (1887); Kohn and Tranton, *J. Chem. Soc.*, **75**, 1155 (1899); Tischtschenko, *Chem. Zentr.*, **77**, 1309, 1552 (1906); Lachman, *J. Am. Chem. Soc.*, **45**, 2356 (1923).

[19] See also Liebig and Wohler, *Ann.*, 3, 266 (1832); Laurent and Gerhardt, *Jahresber.*, **1850**, 489; Schiff, *Ann.*, **154**, 347 (1870); Claisen, *Ber.*, **14**, 2475 (1881).

This product then undergoes an isomeric change and finally gives the ester.

$$C_6H_5CH(OH) - O - CH(ONa)C_6H_5 = C_6H_5CH_2 - O - C(OH)(ONa)C_6H_5$$

$$C_6H_5CH_2 - O - C(OH)(ONa)C_6H_5 = C_6H_5CH_2 - O - COC_6H_5 + NaOH.$$

Condensation of Benzaldehyde to Benzoin

When benzaldehyde is acted on by alkali cyanides, it undergoes a condensation reaction, yielding the substance called benzoin.

$$C_6H_5\dot{C}HO + C_6H_5CHO = C_6H_5CH(OH)COC_6H_5$$

Many explanations [20] have been offered of the mechanism of this reaction, but owing to its complicated nature the mechanism is not yet quite certain in spite of much careful investigation. It seems desirable to give a preliminary discussion of the experimental facts so far ascertained. Bredig and Stern investigated the kinetics of the condensation and found that within wide limits the rate is proportional to the square of the benzaldehyde concentration, for a given concentration of potassium cyanide. The rate is also proportional to the concentration of the catalyst, which was found to be the cyanide ion, CN^-; no benzoin is formed in absence of this ion. Apparently the hydroxyl ion is also necessary because hydrogen cyanide forms no benzoin and the addition of acids stops the condensation; however, hydroxyl ion, in the absence of cyanide ion, fails to form benzoin. The reaction rate is increased when the proportion of water in the solvent is augmented. The action is reversible but the equilibrium is complicated by the presence of side reactions.

It is also necessary to consider an investigation of Lapworth on the addition of hydrogen cyanide to carbon compounds. The rate of the reaction was followed by a color change (see p. 30) and for camphorquinone and hydrogen cyanide in dilute alcohol or aqueous solutions, the following results were obtained: Mineral acids retard the rate of addition very markedly whereas the addition of a base greatly increases the

[20] The earlier literature has been summarized by Stern, *Z. physik. Chem.*, **50**, 513 (1904); Bredig and Stern, *Z. Elektrochem.*, **10**, 582 (1904); Lachman, *J. Am. Chem. Soc.*, **45**, 1529 (1923); *idem, ibid.*, **46**, 708 (1924); Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); Anderson and Jacobson, *J. Am. Chem. Soc.*, **45**, 836 (1923); Engler and Grimm, *Ber.*, **30**, 2921 (1897); Knoevenagel and Tomasczewski, *Ber.*, **36**, 2829 (1903); Claisen, *ibid.*, **20**, 646 (1887); Smith, *Am. Chem. J.*, **22**, 255 (1899); Chalanay and Knoevenagel, *Ber.*, **25**, 293 (1892); Staudinger, *ibid.*, **46**, 3535 (1913); Ultée, *Rec. trav. chim.*, **28**, 1 (1909).

rate; the effect produced is proportional to the strength of the acid or base. Lapworth concluded from these and other results that the reaction velocity depends mainly on the concentration of the cyanogen ions and that the catalytic effect of bases is to be attributed to the increase in concentration of the cyanogen ions. For example, he converted benzaldehyde rapidly into mandelonitrile by shaking it with a cold aqueous solution of potassium cyanide.

Lachman studied the equilibrium between benzaldehyde and benzoin in the absence of solvents and concluded from his own work, as well as previous work by Engler and Grimm and Knoevenagel and Thomasczewski, that the heat decomposition of benzoin is greatly influenced, both qualitatively and quantitatively, by impurities acting as catalysts. Highly purified benzoin at temperatures up to 250° does not decompose at a measureable rate; above this temperature decomposition occurs into a number of products, an appreciable amount of benzaldehyde being formed. Solid potassium cyanide is a good catalyst for the reaction benzoin→benzaldehyde, and at a temperature of about 150°, benzaldehyde may be rapidly distilled from a mixture of benzoin and potassium cyanide, the benzaldehyde being practically the only reaction product. However, if the benzaldehyde is not removed a side reaction occurs and the benzaldehyde yields benzyl benzoate and its hydrolysis products; this reaction, the Cannizzaro reaction, is about equal to the main reaction in extent.

If benzaldehyde is heated with potassium cyanide, both being dry and protected from moisture, no benzoin is formed. If a little water is present, reaction is prompt and yields are good. The same thing occurs if benzoin, instead of water, is added to the benzaldehyde, the concentration of benzoin being increased by heating to 150°. However, heating benzaldehyde either alone or with benzoin does not bring about the change benzaldehyde→benzoin. Benzaldehyde is very resistant to heat but at 300° commences to decompose exclusively in the direction of Cannizzaro's reaction, no benzoin being formed.

Lachman studied the benzaldehyde-benzoin equilibrium in the presence of solvents also and found similar complicating reactions, the work not being in agreement with the results of Anderson and Jacobson. In the presence of both potassium cyanide and potassium hydroxide, benzaldehyde changes partly to benzoin and partly in the direction of Cannizzaro's reaction.

We may now discuss the possible mechanisms for the benzaldehyde-

benzoin reaction. Chalanay and Knoevenagel's hypothesis is based on the following equations:

$$C_6H_5CHO + KCN = HCN + C_6H_5CK(O)$$
$$HCN + C_6H_5CHO = C_6H_5CHOH(CN)$$
$$C_6H_5CK(O) + C_6H_5CHOH(CN) = C_6H_5COCHOHC_6H_5 + KCN.$$

The assumption that benzaldehyde even in dilute solution goes over into a salt of the structure $C_6H_5CK(O)$ makes this hypothesis somewhat unlikely. Lapworth suggested the following hypothesis, based on the tendency of the cyanide ion to form complex ions:

$$C_6H_5CHO + CN^- = [C_6H_5CH(CN)(O)]^-.$$

The mandelonitrile ion adds to a second molecule of benzaldehyde, forming the cyano-benzoin ion:

$$[C_6H_5CH(CN)(O)]^- + C_6H_5CHO = \left[\begin{array}{c} (O) \\ | \\ C_6H_5C-CHC_6H_5 \\ | \quad | \\ CN \quad OH \end{array}\right]^-.$$

This ion loses the $(CN)^-$ ion, giving benzoin and a fresh supply of the catalyst.

Lachman concludes that both the benzoin and Cannizzaro condensations can be accounted for by a single pair of assumptions: (a) benzaldehyde adds MOH to form

$$\begin{array}{c} H \\ | \\ C_6H_5C-OH \\ | \\ OM \end{array} \qquad (A)$$

and in this addition product, OH is the more labile group; (b) benzaldehyde adds hydrocyanic acid to form

$$\begin{array}{c} CN \\ | \\ C_6H_5C-H \\ | \\ OH \end{array} \qquad (B)$$

in which H is the more labile. (A) may react with benzaldehyde by transfer of hydroxyl to yield benzyl benzoate or it may react with (B) to give the alkali cyanide addition product of benzoin. If (A) is absent, as in acidified solutions, benzoin fails to form.

It seems possible to the author that the results obtained in these careful and extensive investigations could also be explained by assuming that benzoin is formed by the interaction of mandelonitrile and benzaldehyde under the influence of the hydroxyl ion although this may

be putting the answers already proposed in a different phrasing. On this assumption we would interpret the necessity for water in the reaction, benzaldehyde $\xrightarrow{KCN}$ benzoin, as being due to the necessity for producing some hydroxyl-ion catalyst rather than entering directly into the reaction.

Transformation of Benzil to Benzilic Acid

When an aqueous solution of benzil is heated, especially in presence of aqueous alkali, it adds a molecule of water and is converted into benzilic acid:

$$C_6H_5COCOC_6H_5 + H_2O = (C_6H_5)_2C(OH)COOH.$$

Lachman [21] who studied this reaction considers that the hydroxyl ion is of comparatively slight importance, since the addition of alkali to water increases the rate only twenty times whereas the hydroxyl ion increased in concentration about 10,000 times. The mechanism of this reaction has long been a matter of speculation and four different hypotheses have been advanced to explain it. Nef assumed an addition of water to benzil, followed by dissociation into benzophenone and "dioxymethylene"; the latter substance, after changing into formic acid, condenses with the benzophenone to yield benzilic acid. Some experiments of Lachman, however, on the decomposition of benzilic acid in aqueous solution, appear definitely to rule out Nef's hypothesis. The benzilic acid decomposes into benzophenone, carbon monoxide, and water, and does not yield any formic acid.

Schroeter has postulated the intermediate formation of diphenyl ketene and potassium hydrogen dioxide. Nicolet and Pelc, however, showed that diphenyl ketene and hydrogen peroxide do not react appreciably in presence of water or alkalis so that Schroeter's assumption must be abandoned. Tiffeneau has suggested that the mechanism is similar to the pinacol-pinacoline change and Michael assumes that the rearrangement is caused by the great positive energy of the alkali. Recently Lachman investigated the problem and suggested the following mechanism in which a molecule of water adds to one of the carboxyl

[21] Lachman, *J. Am. Chem. Soc.*, **44**, 330 (1922). See also Nef, *Ann.*, **298**, 372 (1897); Schroeter, *Ber.*, **42**, 2336 (1909); Nicolet and Pelc, *J. Am. Chem. Soc.*, **43**, 935 (1921); Tiffeneau, *Rev. gen. sci.*, **18**, 584 (1907); Michael, *J. Am. Chem. Soc.*, **42**, 812 (1920); Lieben, *Monatsh.*, **23**, 63 (1902); Meerwein, *Ann.*, **396**, 209 (1913); *idem, ibid.*, **419**, 121 (1919); Klinger, *Ber.*, **19**, 1868 (1886); Lachman, *J. Am. Chem. Soc.*, **45**, 1509 (1923); *idem, ibid.*, **46**, 779 (1924); Scheuing, *Ber.*, **56**, 253 (1923); Schönberg and Keller, *ibid.*, **56**, 1638 (1923).

groups, and one of the hydroxyl groups thus formed exchanges places with a phenyl group:

$$C_6H_5C(OH)_2COC_6H_5 = (C_6H_5)_2C(OH)COOH.$$

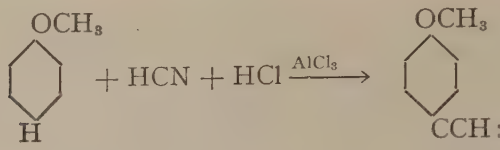
Lachman regards this process as one of intramolecular oxidation and reduction and suggests the term "metakliny" for the phenomenon.

Klinger found that benzil in moist ether when exposed to sunlight gives among other products benzilic acid. The whole situation is somewhat puzzling since the action of light or the hydroxyl ion brings about the change, but the rate is not proportional to the concentration of catalyst. In a further interesting study of the rearrangement Lachman found that benzil forms an addition product with one molecule of sodium ethoxide. In water solution the product breaks down into its components, but in alcohol solution in absence of water it gives only benzaldehyde and ethyl benzoate. When various amounts of water are added to the alcohol solution, the production of benzilic acid increases rapidly. This difference is accounted for by the presence or absence of a mobile hydroxyl group in the intermediate addition products which benzil forms with the reagents: with water, $C_6H_5C(OH)_2COC_6H_5$; with sodium hydroxide, $C_6H_5C(ONa)OHCOC_6H_5$; with sodium ethoxide, $C_6H_5C(ONa)(OC_2H_5)COC_6H_5$. The groups $—OC_2H_5$ and —ONa are incapable of wandering under the experimental conditions.

Preparation of Hydroxy-aldehydes

Gattermann found that phenols can be condensed with hydrogen cyanide, hydrogen chloride and anhydrous zinc chloride to give compounds that hydrolyze readily to form hydroxy-aldehydes. While this is an interesting example of catalysis, most of the published work deals with the preparative technic [22] and not with the mechanism. For some aldehydes it is necessary to replace the zinc chloride by aluminium chloride as condensing agent. The aldehyde group is introduced into monohydric phenols in the *para*-position if this is occupied by hydrogen, the *p*-hydroxy-aldehydes being formed in 50 per cent to 90 per cent yield; if the *para*-position is already occupied by a substituting group, *o*-hydroxy-aldehydes are formed in small yields in the benzene series, but readily in the β-napthols. Since phenolic ethers may be employed the hydrogen cyanide presumably adds directly to form an imide hydrochloride.

[22] Gattermann, *Ber.*, **31**, 1765 (1898); *idem, ibid.*, **32**, 278, 284 (1899); *idem, Ann.*, **357**, 313 (1907); Morgan and Vining, *J. Chem. Soc.*, **119**, 177 (1921); Karrer, *Helvetica Chim. Acta*, **2**, 89 (1919); Adams and Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923); Adams and Montgomery, *ibid.*, **46**, 1518 (1924).



The Perkin Condensation

Perkin found that heating benzoic aldehyde with acetic anhydride and sodium acetate gave cinnamic acid. This synthesis can be carried out with substituted benzaldehydes on the one hand and with homologs of acetic acid or dibasic acids on the other. Its mechanism has been the subject of much discussion.[23] Perkin himself found that the sodium acetate could be replaced by lead acetate, sodium butyrate or sodium valerate, in all cases cinnamic acid being formed, so that he regarded the formation of the acid as being due to reaction between the aldehyde and the anhydride, the sodium salt acting presumably as a catalyst. The proportions of reactants he employed were one part of sodium acetate, two of aldehyde and three of anhydride; he found that using a greater proportion of sodium acetate did not increase the yield, whereas diminishing the proportion of acetate diminished the yield.

Fittig concluded that the reaction occurred between the aldehyde and the sodium salt, because mixtures of aldehyde, acetic anhydride and sodium butyrate could be made to yield phenyl angelic acid. He neglected to take into account the equilibrium between acetic anhydride and sodium butyrate. Michael and Hartman showed that his mixtures must have contained considerable butyric anhydride and sodium acetate and little if any acetic anhydride and sodium butyrate.

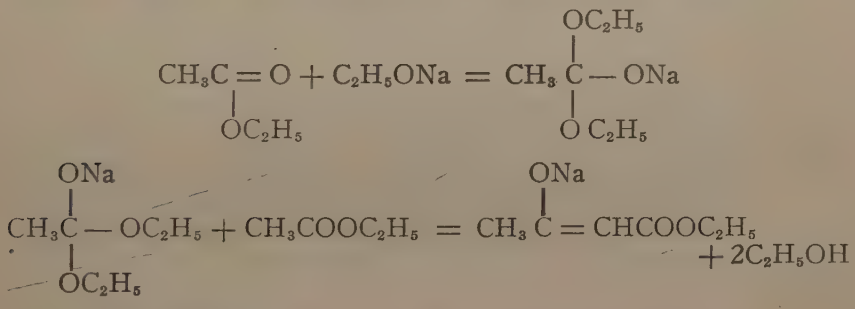
Meyer and Beer also conclude that the acid anhydride is not one of the reactants. They found that benzaldehyde, acetic acid and potassium acetate gave cinnamic acid, and they regard this as evidence that the acid anhydride is not essential in the Perkin reaction. Bakunin and Fisceman have discussed this condensation and emphasize the importance of taking into account the equilibrium between the acetic anhydride and the sodium salt. They regard the function of the acetic anhydride as being largely a dehydrating agent for dissolving the reacting substances.

[23] Perkin, *J. Chem. Soc.*, **31**, 388 (1877); Fittig and Slocum, *Ann.*, **277**, 53 (1885); Fittig, *ibid.*, **277**, 48 (1885); Nef, *ibid.*, **298**, 202 (1897); Michael and Hartman, *Ber.*, **34**, 918 (1901); Meyer and Beer, *Monatsh.*, **34**, 649 (1913); Michael, *Am. Chem. J.*, **50**, 411 (1913); Bakunin and Fisceman, *Gazzetta*, **46**, 77 (1916); Reich and Chaskelis, *Bull. Soc. chim.*, **19**, 287 (1916).

It would seem that a kinetic study of the Perkin condensation is necessary to find how the rate of the reaction is affected by the concentrations of the various reactants. This should give the necessary information to determine the actual mechanism of the reaction.

The Claisen Condensation

The Claisen condensation in its most general form may be considered to include the condensation of carboxylic esters with a ketone or carboxylic ester in the presence of sodium ethoxide, sodamide, sodium or similar agents. The question of its mechanism has been the subject of much controversy and is associated with numerous investigations.[24] Geuther originally prepared acetoacetic ester by the action of metallic sodium on ethyl acetate and this action was explained by Frankland and Duppa by means of a mechanism involving the assumption of the primary formation of sodium acetic ester, $CH_2NaCOOEt$. Claisen rejected this view and suggested in its place that Geuther's reaction is due not to the direct action of sodium but to that of sodium ethylate, which forms an addition product with the ethyl acetate, and that this reacts with more of the ethyl acetate to form acetoacetic ester, thus:



[24] Geuther, *Jahresber.*, **1863**, 323; Frankland and Duppa, *Phil. Trans.*, **156**, 37 (1866); *idem, Ann.*, **138**, 204 (1866); v. Baeyer, *Ber.*, **18**, 3460 (1885); Wislecenus, *Ann.*, **186**, 163 (1877); Claisen and Lowman, *Ber.*, **20**, 651 (1887); *idem, ibid.*, **21**, 1154 (1888); Brömme and Claisen, *ibid.*, **21**, 1132 (1888); Claisen, *ibid.*, **27**, 114 (1895); *idem, ibid.*, **38**, 708 (1905); *idem, Ann.*, **277**, 184 (1893); *idem, ibid.*, **291**, 25 (1896); *idem, ibid.*, **297**, 92 (1897); Michael, *J. pr. Chem.*, **37**, 507 (1888); *idem, Ber.*, **33**, 3731 (1900); *idem, ibid.*, **38**, 1922 (1905); Nef, *Ann.*, **298**, 319 (1897); Dieckmann, *Ber.*, **33**, 2670 (1900); Lapworth, *J. Chem. Soc.*, **79**, 1269 (1901); *idem, ibid.*, **81**, 1512 (1902); *idem, ibid.*, **40**, 46 (1908); Clarke, Lapworth and Wechsler, *ibid.*, **93**, 30 (1908); Tingle and Gorsline, *Am. Chem. J.*, **37**, 483 (1907); Clark, *J. Phys. Chem.*, **12**, 1 (1908); Dieckmann and Kron, *Ber.*, **41**, 1260 (1908); Johnson and Hill, *J. Am. Chem. Soc.*, **35**, 1023 (1913); Morgan, Drew and Porter, *Ber.*, **58**, 333 (1925); Scheibler and Voss, *Ber.*, **53**, 388 (1920); Scheibler and Zeigner, *ibid.*, **55**, 789 (1922); Scheibler and Schmidt, *ibid.*, **58**, 1189 (1925); Scheibler and Friese, *Ann.*, **445**, 141 (1925); Scheibler, Marhenkel and Bassanoff, *Ber.*, **58**, 1198 (1925).

It must be admitted that the evidence is fairly strong that the sodium acts merely by removing the alcohol and by keeping the reaction mixture dry. Clark, in the course of a kinetic study of the reaction between ethyl oxalate and acetone catalyzed by sodium ethylate, found that traces of water greatly retard the reaction. When the reaction is performed in alcoholic solution, Clark found that for the more dilute solutions the rate is proportional to the concentration of acetone and to the square of the concentrations of both the oxalic ester and sodium ethylate; in stronger solutions the rate is still proportional to the concentration of acetone but is proportional to powers between one and two, of the other reactants. These experiments constitute strong evidence as to the correctness of some such scheme of double compound formation as suggested by Claisen or by Nef.

Tingle and Gorsline found that both ether and tertiary bases catalyze the reaction, which suggests the possibility that the primary reaction of double compound formation is followed by a catalytic decomposition by the hydroxyl ion. In this connection it may be mentioned that Johnson and Hill found that ethyl acetate acts as a catalyst in the action of sodium on ethyl phenoxyacetate which undergoes a Claisen condensation when acted on by sodium. It does not seem possible to decide whether the ethyl acetate takes part directly in the reaction or merely acts as a solvent favoring the active catalyst. Tingle and Gorsline favor the explanation advanced by Michael in which the sodium is regarded as first acting on the ethyl acetate:

$$CH_3COOC_2H_5 + Na = CH_2NaCOOC_2H_5 + \tfrac{1}{2}H_2.$$

A second molecule of ethyl acetate then adds to the enolic form of the sodium derivative:

$$CH_3COOC_2H_5 + \underset{\underset{ONa}{|}}{CH_2}\,CO\,C_2H_5 = \underset{\underset{ONa}{|}}{\overset{\overset{CH_2COOC_2H_5}{|}}{CH_3\,C}}\,O\,C_2H_5,$$

after which alcohol is eliminated, giving the product $CH_3C(ONa):CHCOOC_2H_5$. The recent work of Scheibler and his collaborators strongly supports some such mechanism as this.

While there have been several other mechanisms suggested and the Claisen mechanism has been subjected to much criticism, these other suggestions have resulted from qualitative studies of more complicated reactions which are sometimes of such a nature as to exclude the origi-

nal explanation. In a recent paper by Morgan, Drew and Porter it has been shown that in a number of examples the normal Claisen condensation occurs between esters and ketones at low temperatures whereas alcoholysis takes place at higher temperatures with consequent decomposition of the αγ-diketone.

The Michael Reaction

Although the condensation of $\alpha\beta$-unsaturated esters with sodium derivatives of the type of ethyl malonate, generally known as the Michael reaction, is one of the most valuable methods of synthesis in the hands of the organic chemist, its mechanism[25] has received until recently comparatively little attention. Michael originally studied the condensatoin of ethyl cinnamate with ethyl malonate to give ethyl decomposition of the $\alpha\gamma$-diketone.

$$C_6H_5CH:CHCOOEt + CH_2(COOEt)_2 \rightleftarrows C_6H_5CH\begin{cases} CH(COOEt)_2 \\ CH_2COOEt. \end{cases}$$

Another early study was by Perkin and Thorpe who found that ethyl dimethylacrylate undergoes this type of condensation with ethyl cyanoacetate. The early workers found that the yields were very variable and seldom good, usually being between 20 and 60 per cent. It was early recognized that the reaction is catalytic, since Knoevenagel and Mottek first showed that piperidine is a powerful catalyst for the Michael condensation and in many instances can be used with advantage in place of the sodium ethoxide more commonly employed; presumably therefore the reaction is an example of hydroxyl-ion catalysis, being favored by such conditions as lead to a high concentration of this catalyst.

Recently Ingold and Thorpe and their co-workers have made a study of this reaction and have established the interesting fact that it is reversible and that the low yields obtained in many instances are due to this. The direct condensation is apparently an exothermic process since low temperature greatly increases the equilibrium concentration of the product. Furthermore, the acetic ester which takes part in a condensation must contain a negative substituent, the cyano-group being far more effective than the carboethoxy-group. The acrylic ester also

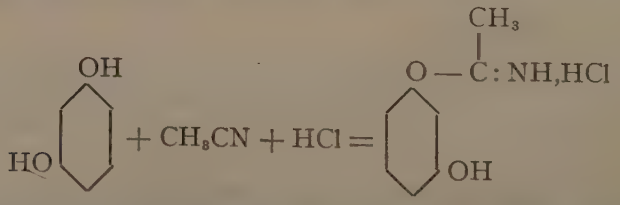
[25] Michael, *J. pr. Chem.*, **35**, 351 (1887); *idem, Ber.*, **33**, 3731 (1900); Knoevenagel and Mottek, *ibid.*, **37**, 4464 (1904); Perkin and Thorpe, *J. Chem. Soc.*, **75**, 51 (1899); Ingold and Powell, *ibid.*, **119**, 1976 (1921); Ingold, Perrin and Thorpe, *ibid.*, **121**, 1765 (1922); Ingold and Perrin, *ibid.*, **121**, 1416 (1922).

should be but lightly substituted since both α and β substituents reduce the tendency to condensation, the effect being apparently a spatial one.

It would seem that a possible mechanism for the Michael condensation consists of a preliminary slow reaction between the malonic ester (or other similar ester) and the hydroxyl ion with possibly formation of a fugitive complex, followed by a very rapid reaction between the complex and the acrylic ester. The rate of the reaction should therefore be proportional to the concentration of the malonic ester and to the concentration of catalyst but should be independent of the concentration of acrylic ester. It is evident that the yields considered on the basis of acrylic ester added will be greatly increased by using less than the theoretical proportion of acrylic ester; an experiment of Ingold and Powell (see reference, p. 1980) supports this. It should be noted that the equilibrium conditions may be quite different in the Michael reaction according as sodium ethylate or piperidine is used as catalyst, because in the former case we are using the sodium salts and in the latter case the free esters.

Hoesch's Synthesis

Hoesch's [26] synthesis is based on the production of a ketone-imide hydrochloride of the type $\begin{matrix} R \\ R' \end{matrix}\!\!>\!C\!:\!NH,HCl$ by condensation of nitriles with phenols by hydrogen chloride in presence of zinc chloride and ether. Thus on treating resorcinol and acetonitrile in ethereal solution with zinc chloride and hydrochloric acid, the ketone-imide begins to separate in half an hour and a 70 per cent yield is obtained.



The ketone-imide may easily be hydrolyzed to give the ketone resacetophenone. It would be interesting to know the mechanism of this reaction. Apparently all we can say at present is that it is an example of hydrogen-ion catalysis. As is usual in these reactions the substances

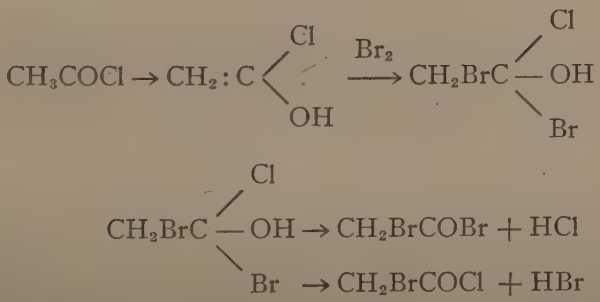
[26] Hoesch, *Ber.*, **48**, 1122 (1915); Slater and Stephen, *J. Chem. Soc.*, **117**, 309 (1920).

must be dry since water acts as a strong negative catalyst. The action of the zinc chloride is not clear; it can be omitted in a great many of the syntheses without impairment of the yield.

The Hell-Volhard Reaction

The mechanism of the reaction for the preparation of α-bromoacids by the Hell-Volhard method has been the subject of considerable discussion.[27] Bromine scarcely acts on acetic acid even at its boiling point, and Lapworth found that even when saturated with hydrogen chloride or bromide, acetic acid containing 1 or 2 per cent of water is only slowly attacked by the halogen at 100°. However, if the water is removed from the acetic acid by repeated freezing or the addition of acetyl chloride, bromine reacts readily in the presence of hydrogen chloride. It may be noted here that acetic anhydride requires an acid catalyst such as hydrogen chloride or sulfuric acid to catalyze the reaction with bromine.

The mechanism of the bromination of acids in the α-position in the presence of red phosphorus has been supposed to necessitate the preliminary formation of the acid bromide, which is then brominated with comparative ease. Aschan suggested that the reaction is not one of direct substitution but consists essentially in the addition of bromine to an enolic form, with subsequent loss of hydrogen bromide according to the following scheme:



He supported this suggestion by brominating acetyl chloride, when bromoacetyl chloride and bromoacetyl bromide were produced, a mixture of hydrogen chloride and hydrogen bromide being evolved. A similar result was obtained by Smith and Lewcock in their investigation

[27] Lapworth, *J. Chem. Soc.*, **85**, 41 (1904); Aschan, *Ber.*, **45**, 1913 (1912); *idem, ibid.*, **46**, 2162 (1913); Smith and Lewcock, *ibid.*, **45**, 2358 (1912); Meyer, *ibid.*, **45**, 2864 (1912); Ward, *J. Chem. Soc.*, **121**, 1161 (1922); Shaw, *ibid.*, **123**, 2233 (1923).

of the action of bromine on isobutyryl chloride, in this case the brominated product consisting almost entirely of α-bromoisobutyryl bromide.

Meyer pointed out that these experiments are quite inconclusive because of the equilibrium,

$$CH_3BrCOCl + HBr \rightleftarrows CH_2BrCOBr + HCl,$$

which would yield mixtures of the two acids no matter what the method of substitution is. Indeed Staudinger and Anthes [28] were able to obtain theoretical yields of acid bromides by passing hydrogen bromide through the heated acid chlorides. Meyer concluded from his experiments on the bromination of malonic acid (see p. 97), in which the rate is independent of the bromine concentration, that in the Hell-Volhard bromination, enolization first occurs.

In a recent paper Ward has reported performing the Hell-Volhard reaction using only a small proportion of red phosphorus (2 per cent in most cases) and obtained good yields of the α-bromo-acids. He concludes that the phosphorus does not act as a "carrier" but forms phosphorus tribromide and this acts on any water which may be present or on the acid, generating hydrobromic acid which catalyzes the reaction. He showed that bromine and dry acetic acid give good yields of the bromo-acid in presence of hydrogen bromide as a catalyst.

It is evident that much more light could be thrown on the Hell-Volhard reaction by a kinetic study and this has been done in a recent paper by Shaw. He points out that the time required for complete bromination of dry acetic acid saturated with hydrogen chloride is much longer than when phosphorus is employed. Shaw measured the rate of disappearance of bromine in a large excess of acetic acid in presence of hydrogen chloride, phosphorus tribromide, acetyl chloride, and acetic anhydride. In presence of hydrogen chloride the rate was independent of the bromine concentration; in presence of acetic anhydride the rate was proportional to the concentration of the bromine; in presence of phosphorus tribromide or acetyl chloride the initial rate was very rapid but fell off quickly as the bromine concentration diminished.

In the experiments using acetic anhydride the rate was proportional to the concentration of anhydride; furthermore, the presence of hydrogen chloride greatly diminished the rate of the reaction. It is evident therefore that acetic anhydride plays a very important part in the reaction and the action of hydrogen chloride on it may be explained by considering the following equilibrium,

[28] Staudinger and Anthes, *Ber.*, **46**, 1417 (1913).

$$(CH_3CO)_2O + HCl \rightleftarrows CH_3COCl + CH_3COOH,$$

which would lead to removal of the anhydride. In order to explain the action of the acetic anhydride Shaw uses a mechanism first proposed by Hentschel:[29]

$$(CH_3CO)_2O + Br_2 = CH_3COBr + CH_2BrCOOH,$$

$$CH_3COBr + CH_3COOH \rightleftarrows (CH_3CO)_2O + HBr.$$

The first reaction is very rapid since acetic anhydride and bromine react completely in a few seconds at 100°, if a catalyst such as a trace of hydrogen chloride is present. It is probable that this reaction involves an enolic change in the acetic anhydride since Orton and Jones[30] have shown that the rate of reaction between bromine and acetic anhydride is independent of the bromine concentration. The second reaction is reversible but will proceed to completion because the anhydride is removed by the first reaction. It is evident then that this mechanism provides a fairly satisfactory explanation of the experimental results. When acetic acid is brominated in presence of red phosphorus the reaction at first proceeds entirely through the anhydride, but as the concentration of bromine diminishes and that of hydrogen bromide increases, the rate of reaction through the enolic form of the acid will increase, until at the end the reaction proceeds entirely in this way.

[29] Hentschel, *Ber.*, **17**, 1286 (1884).
[30] Orton and Jones, *J. Chem. Soc.*, **101**, 1723 (1912).

Chapter X.

Special Topics.

A number of molecular rearrangements of great interest to organic chemists are treated in this chapter, together with several other special topics in the field of work which correlates chemical reactivity and structure.

The Walden Inversion

Walden, while investigating the optically active modifications of halogen-substituted succinic acids, was led to the wholly unexpected conclusion that in certain reactions it is possible to convert an active compound containing an asymmetric carbon atom into its enantiomeride directly, without racemizing it, and then resolving the racemic compound. Phenomena of this character have been grouped together under the designation "The Walden Inversion" around which an extremely extensive literature [1] has grown, although up to the present no generally accepted theoretical explanation has been found.

[1] Walden, *Ber.*, **28**, 1287 (1895); *idem, ibid.*, **29**, 133 (1896); *idem, ibid.*, **30**, 3146 (1897); *idem, ibid.*, **32**, 1833 (1899); Walden and Lutz, *ibid.*, **30**, 2795 (1897); Fisher, *ibid.*, **39**, 2895 (1906); *idem, ibid.*, **40**, 489, 502 (1907); Fisher and Raske, *ibid.*, **40**, 1052 (1907); Fisher and Schoeller, *Ann.*, **357**, 11 (1907); Fisher and Scheibler, *Ber.*, **41**, 889, 2891 (1908); *idem, ibid.*, **42**, 1219 (1909); McKenzie and Wren, *J. Chem. Soc.*, **97**, 1355 (1910); McKenzie and Clough, *ibid.*, **97**, 1016, 2566 (1910); McKenzie and Humphries, *ibid.*, **97**, 121 (1910); Fisher, Scheibler and Groh, *Ber.*, **43**, 2020 (1910); Fisher and Scheibler, *Ann.*, **383**, 337 (1911); Fisher, *ibid.*, **381**, 123 (1911); McKenzie and Barrow, *J. Chem. Soc.*, **99**, 1910 (1911); Werner, *Ber.*, **44**, 873 (1911); *idem, Helv. Chim. Acta*, **1**, 5 (1918); Pfeiffer, *Ann.*, **383**, 123 (1911); Biilmann, *Ann.*, **388**, 330 (1912); Gadamar, *Chem. Zeit.*, **36**, 1327 (1912); Senter, *J. Chem. Soc.*, **91**, 460 (1907); *idem, ibid.*, **95**, 1827 (1909); *idem, ibid.*, **97**, 346 (1910); *idem, ibid.*, **99**, 95 (1911); *idem, Z. physik. Chem.*, **70**, 511 (1910); *idem, Ber.*, **45**, 2318 (1912); Holmberg, *Ber.*, **45**, 1713, 2997 (1912); Frankland, *J. Chem. Soc.*, **103**, 713 (1913); Senter and Drew, *ibid.*, **107**, 638 (1915); *idem, ibid.*, **109**, 1091 (1916); Frankland and Garner, *ibid.*, **105**, 1101 (1914); Holmberg, *Arkiv. Kem. Min. Geol.*, **6**, No. 8 (1916); Senter and Tucker, *J. Chem. Soc.*, **109**, 690 (1916); Senter and Martin, *ibid.*, **111**, 447 (1917); Clough, *ibid.*, **113**, 526 (1918); Senter and Tucker, *ibid.*, **113**, 140 (1918); Senter, Drew and Martin, *ibid.*, **113**, 151 (1918); Karrer and Kaase, *Helv. Chim. Acta*, **2**, 436 (1919); *idem, ibid.*, **3**, 244 (1920); Erlenmeyer, *Biochem. Zeitsch.*, **97**, 255 (1919); Clough, *Helv. Chim. Acta*, **3**, 233 (1920); Uspeński, *J. Russ. Phys. Chem. Soc.*, **51**, 275 (1920); Phillips, *J. Chem. Soc.*, **123**, 44 (1923); Levene and Mikeska, *J. Biol. Chem.*, **59**, 473 (1924); *idem, ibid.*, **60**, 1, 685 (1924); McKenzie and Tudhope, *ibid.*, **62**, 551 (1924); Senter and Ward, *J. Chem. Soc.*, **125**, 2137 (1924); *idem, ibid.*, 127, 1847 (1925); Kenyon, Phillips and Turley, *ibid.*, **127**, 399 (1925); Terry and Eichelberger, *J. Am. Chem. Soc.*, **47**, 1067 (1925).

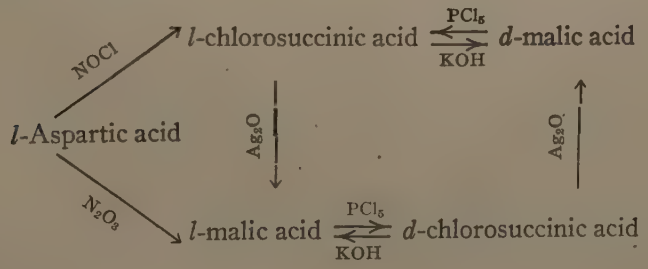
In his original work Walden first converted *l*-aspartic acid, $COOHCH(NH_2)CH_2COOH$, into *l*-malic acid by the action of nitrous acid, and then converted the *l*-malic acid into *d*-chlorosuccinic acid by the action of phosphorus pentachloride. When *l*-aspartic acid is converted directly into chlorosuccinic acid by nitrosyl chloride the levo-modification is produced. Thus not only levo-rotatory but also dextro-rotatory chlorosuccinic acid can be obtained from one and the same levo-rotatory aspartic acid, according as the amino group is replaced by chlorine by means of nitrosyl chloride, or is first replaced by hydroxyl by means of nitrous acid, the hydroxyl being subsequently replaced by chlorine, using phosphorus pentachloride.

These processes occur in two stages, and at one of the stages an "abnormal reaction" occurs, resulting in a change of configuration. It is not possible at present to decide at which stage this change takes place because the sign of rotation of the product cannot be relied upon to decide this. Many instances are known in which substitution occurs remote from the asymmetric carbon atom, yet produces a reversal of sign. In such cases no change of configuration can be assumed, and therefore it is evident that change of sign does not necessarily coincide with a change in configuration.

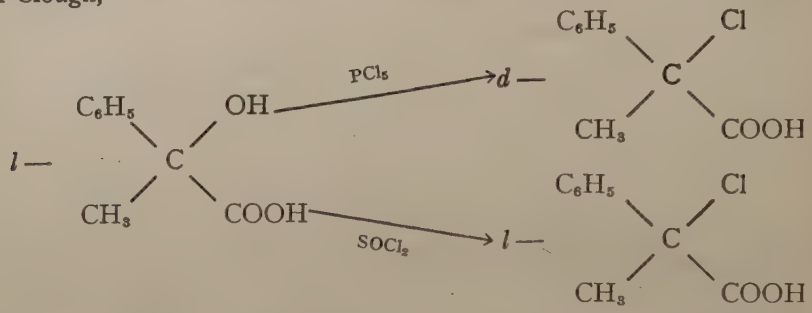
Walden also showed that different enantiomerides of malic acid could be obtained from the chlorosuccinic acids simply by altering the reagent by which the replacement of hydroxyl was effected, thus:

$$\left.\begin{matrix} l\text{-chlorosuccinic} \\ \\ d\text{-chlorosuccinic} \\ \\ \end{matrix}\right\} \begin{matrix} + Ag_2O = l\text{-malic acid} \\ + KOH = d\text{-malic acid} \\ + Ag_2O = d\text{-malic acid} \\ + KOH = l\text{-malic acid} \end{matrix}$$

He found that, although exceptions occur, as a rule strong bases cause a reversal of the rotatory power, while feeble bases give a malic acid of similar sign. The position reached by Walden can be summarized in the following scheme:



Several such optical cycles of changes have been accomplished, during which a change of configuration occurs. It is evident that change of configuration does not necessarily accompany any particular reaction, but that the catalyst or reagent effecting it plays an important part. This is shown very beautifully in a reaction investigated by McKenzie and Clough,



This reaction is free from the objection that may be urged against the use of silver oxide in the replacement of the bromine atom in, for example, *l*-α-bromopropionic acid. The silver salt of this acid in aqueous solution rapidly eliminates silver bromide; thus it is possible that comparisons of silver oxide with other alkalis is not justified. On the other hand slight alterations in the groups attached to the asymmetric carbon atom cause reactions to proceed in optically different manners. Fisher showed that when *d*-alanine ethyl ester is acted on by nitrosyl bromide, bromopropionic acid is formed.

Most cases of the Walden inversions have been observed in transformations of α-substituted acids and their derivatives, which are much more readily obtained and react more easily than the corresponding β-derivatives. It seemed possible therefore that the change in configuration is due either to the presence of a hydrogen atom attached to the asymmetric carbon atom or to the fact that the optically active compounds in question were carboxylic acids. Although the transformation may be due to one or both of these causes, in certain cases it has been shown by Fisher that acids containing an optically active carbon atom in the β position also undergo the Walden inversion. McKenzie and Clough have also shown that it can occur in compounds which do not contain a carboxyl group.

The early views in the mechanism of the reaction were put forward by Fisher, Werner, Pfeiffer, Biilmann, Gadamar, Frankland, Holmberg and Senter; much of Senter's work was on the rate of hydrolysis of

halogen-substituted acids. Since these views were put forward there has been considerable additional information available as for example the work of Senter and Drew on the reaction between *d*- and *l*-phenylchloro-acetic acids and ammonia. They confirmed the results of previous observers that in aqueous solution the reaction is attended with considerable racemization and that the resulting phenylamino-acetic acid has the opposite sign to the phenylchloro-acetic acid taken. With acetonitrile as solvent there is also considerable racemization, but the resulting amino-acid has the same sign as the phenylchloro-acetic acid taken; this result was confirmed by starting both with *d*- and with *l*-phenylchloro-acetic acid.

A remarkable fact in the experiments with acetonitrile as solvent is that the proportion of active phenylamino-acetic acid in the product is practically independent of the temperature at which the reaction is carried out, being almost the same at 9° and at 52°. On the other hand, the amino-acid obtained from solutions in water and in methyl alcohol at 52° was quite inactive, while an acid of considerable activity was obtained from an aqueous solution at 9°. In later work the number of solvents was greatly extended and the results showed that inversion occurred in about half of the examples studied; also the curious result was obtained that the amino-acid produced from *l*-phenylbromo-acetic acid is opposite in sign according as the displacement is carried out in water or alcoholic solution, but if *l*-phenylchloro-acetic acid is used, the amino-acid has the same sign in both solvents.

Frankland and Garner have pointed out that in order to convert an optically active compound into its enantiomorph, at least two steps are necessary, and it is at present uncertain in which of the two steps the change of configuration occurs. There does not exist at the present time any criterion whereby the relation between the configuration of an optically active compound and that of a derivative from it can be decisively ascertained. A regularity which appears to emerge from a study of the recorded phenomena is that an optically active hydroxy-compound is invariably converted into its enantiomorph when thionyl chloride and silver oxide are successively employed as reagents. All other similar pairs of reagents behave irregularly. Clough's paper contains a good discussion of these irregularities and suggests possible means of determining at which stage inversion occurs, through a study of the configuration of similarly constituted compounds.

Another attempt to devise a method whereby a change in configuration as distinguished from a change in sign can be detected with cer-

tainty was made by Karrer and Kaase, by measuring the optical rotations of a series of compounds for light of different wave-lengths. Phillips has also studied the problem by carrying out a series of substitutions, in some of which only part of a group attached to an asymmetric carbon atom was replaced. He assumes that in such substitutions the configuration of both compounds is the same, independently of any change in optical rotation. One remarkable reaction studied in this paper was the following:

The results showed that inversion of configuration had taken place to the extent of 98.7 per cent, which is remarkable for its completeness.

Terry and Eichelberger have studied the bromination of fumaric and maleic acids and have concluded that these reactions have much in common with the Walden inversion. When there is addition at the double bond of maleic acid we should obtain the *meso*-form of the resultant substituted succinic acid, whereas from fumaric acid we should obtain the racemic form. When the neutral salts are oxidized by permanganate the tartaric acids obtained are exactly those demanded by theory, whereas when bromine is added to the acids the resultant dibromosuccinic acids have not the theoretical configuration. When bromine is added to the neutral salts maleic acid gives 80 per cent of the expected dichlorosuccinic acid but fumaric acid gives only 10 per cent of the expected *iso*-dichlorosuccinic acid. Terry and Eichelberger put forward a mechanism for these reactions (see p. 100) and suggest that the mechanism of the Walden inversion may be similar since the formation of unsaturated substances has often been observed in the inversion.

From this review we must conclude regretfully that chemical methods alone, in spite of the enormous amount of work done, do not appear to be sufficient to explain and predict the many vagaries that occur when studying the Walden inversion. Undoubtedly the most serious difficulty lies in determining the actual configuration apart from a change in sign, and none of the chemical methods devised for this purpose are entirely satisfactory. A physical method such as the X-ray studies of *d*-tartaric acid and racemic acid made by Astbury [2] would give us a method free from any suspicion that a configurative inversion

[2] Astbury, *Proc. Roy. Soc.*, **102**, 506 (1922); *idem, ibid.*, **104**, 219 (1923).

had occurred during the process of replacing atoms or groups, even those not directly attached to the asymmetric carbon atom.

The Beckmann Inversion

When ketoximes are treated with reagents such as phosphorus chloride, concentrated sulfuric acid, or a mixture of acetic acid, acetic anhydride and hydrochloric acid (Beckmann's mixture), they undergo a remarkable intramolecular transformation, called after its discoverer [3] the Beckmann rearrangement. Ketoximes yield substituted acid amides, the action in the case of benzophenone being represented as follows:

$$(C_6H_5)C{:}NOH = C_6H_5CONHC_6H_5.$$

Considerable rearrangement of the molecule takes place, including the migration of an aryl group from carbon to nitrogen. Beckmann himself considered the rearrangement to be simply a direct interchange of radicals as shown in the following scheme:

$$C_6H_5C(C_6H_5)(NOH) \longrightarrow C_6H_5C(OH)(NC_6H_5) \longrightarrow C_6H_5C(=O)(NHC_6H_5).$$

The reagents are considered to be catalysts and Beckmann has given no further account of how they work. The mechanism of this change has been the subject of an extremely voluminous discussion but even yet the course of the change is not entirely clear. Stieglitz,[4] in a long series of papers, has made a detailed study of the reaction and has concluded that at one stage of the reaction a compound is produced having free residual valencies, and this substance can undergo hydrolysis in the usually accepted manner with formation of an amide. The first step, according to Stieglitz's view, is the formation of a salt, which is then dehydrated by the action of the reagents:

$$C_6H_5C(C_6H_5)(HCl\,N\,OH) = C_6H_5C(C_6H_5)(N\,Cl) + H_2O$$

The hydroxyl group of the salt is positive and in the removal of water it must capture two electrons from the nitrogen. The nitrogen, in turn, takes away two electrons from the carbon and this leads to a rearrangement resulting in a more stable system:

[3] Beckmann, *Ber.*, **27**, 300 (1894).
[4] See especially Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 272, 607 (1914); Stieglitz, *ibid.*, **44**, 1477 (1922).

$$C_6H_5\,C\,C_6H_5 \;\;\underset{NCl}{\|} \;=\; C_6H_5\,C \;\;\underset{N\;Cl\,C_6H_5}{|||} \;=\; C_6H_5\,C\,Cl \;\;\underset{N\,C_6H_5}{\|}$$

Finally, the chloroacid-imide whose formation has just been indicated, and which can be actually isolated, is transformed upon treatment with water into benzanilide:

$$C_6H_5\,C\,Cl \;\;\underset{N\,C_6H_5}{\|} + H_2O = C_6H_5\,C\,OH \;\;\underset{N\,C_6H_5}{\|} + HCl = C_6H_5\,C\,O \;\;\underset{NH\,C_6H_5}{|}.$$

Lachman [5] in some recent work has considered critically the previous explanations for the mechanism of this reaction and has done some very significant experiments which it seems well to discuss at this point. Benzophenone-oxime was used in the experiments, in the first of which he examined the effect of heat on the substance in absence of air. The course of the reaction is represented as follows:

$$2\,(C_6H_5)_2C{:}\,NOH = (C_6H_5)_2CO + (C_6H_5)_2C{:}\,NH + (NOH).$$

The NOH decomposes into nitrogen, oxides of nitrogen and water; the water is taken up by the imidodiphenyl methane (benzophenone-imide) which hydrolyzes readily into benzophenone and ammonia.

$$(C_6H_5)_2C{:}\,NH + H_2O = (C_6H_5)_2CO + NH_3.$$

No benzanilide is formed, so that we can conclude that the Beckmann rearrangement does not occur when benzophenone-oxime is heated alone. It may be of course that the change to the ketone and imide is very rapid as compared with the rearrangement, and it is difficult to see how this possibility can be eliminated without making actual rate measurements; furthermore it must be remembered that the change of the oxime to ketone and imide may be determined by an alkaline catalyst whereas the rearrangement may require an acid catalyst.

The next experiment was designed to test the effect of hydrochloric acid on benzophenone-oxime. Kuhara [6] showed that the hydrochloride salt of the oxime undergoes complete rearrangement at 110°-120° and Lachman extended this work by heating the oxime in presence of various proportions of the hydrochloric salt. He found that very small proportions of the salt would bring about the rearrangement. In a final experiment he studied the effect of heating the salt in presence of

[5] Lachman, *J. Am. Chem. Soc.*, **46**, 1477 (1924); *idem, ibid.*, **47**, 260 (1925).
[6] Kuhara, *Min. Coll. Sci. Imp. Kyoto Univ.*, **3**, 1 (1917); see also Lehmann, *Z. angew. Chem.*, **36**, 360 (1923).

water and considered the various equilibria in the solution. The formation of benzophenone-oxime according to the equation

$$(C_6H_5)_2CO + NH_2OH + HCl \rightleftarrows (C_6H_5)_2 C:NOH + H_2O$$

is a reversible process. An increase of hydrochloric acid concentration shifts the equilibrium to the left since hydroxylamine is a stronger base than the oxime. In alkaline media the reaction proceeds quantitatively to the right.

A second state of equilibrium according to the equation,

$$(C_6H_5)_2C:NOH + HCl \rightleftarrows (C_6H_5)_2C:NOH,HCl$$

arises from the weakly basic nature of benzophenone-oxime, this salt being largely hydrolyzed by water. In anhydrous solvents, salt formation is quantitative. Lachman found that the rearrangement to benzanilide took place even in presence of water if due regard were had for the foregoing considerations. These experiments would appear definitely to dispose of the hypothesis that dehydration is a necessary step in the Beckmann transformation, at any rate for benzophenone-oxime. Lachman concludes from his work that benzophenone-oxime does not rearrange at all, but its salts do; the fundamental process is therefore represented as the direct conversion of the oxime salt into an acid imide and a free acid:

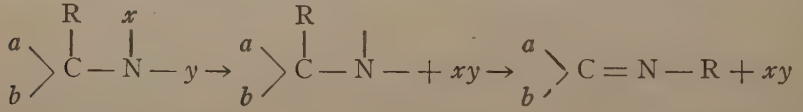
$$(C_6H_5)_2C:NOH,HCl = C_6H_5CONHC_6H_5 + HCl.$$

The acid liberated by this reaction re-enters the cycle with a fresh portion of oxime and is thus strictly a catalytic agent. The function of a dehydrating agent is merely to furnish an anhydrous medium, which is a prerequisite to the formation of oxime salts.

It does not seem to be established completely and unequivocally, however, that it is the hydrochloride that undergoes the rearrangement and we may therefore consider another possible mechanism that is more in line with other examples of isomeric change. We may regard the oxime merely as a solvent for the hydrochloric acid, the liquid mixture containing free oxime, the oxime salt (solvated HCl), undissociated acid and hydrogen and chlorine ions. The action may then be regarded as simple hydrogen-ion catalysis. It does not seem possible without making a kinetic study of the reaction to determine whether the free oxime or its salt or both rearrange on collision with a hydrogen ion. From this point of view the rôle of water also becomes clear because the negative catalytic effect of water on hydrogen-ion catalysis in organic solvents is well known.

Considerable uncertainty has been introduced as to the mechanism of the Beckmann change by recent work on the structure of isomeric oximes. Hantzsch originally used [7] the rearrangement for determining the spatial structure of oximes by assuming that the two radicals in the "syn" position interchanged, whereas commencing with Meisenheimer's work [8] considerable evidence has been developed [9] that the Beckmann change takes place in a *trans* and not in a *cis* manner. At present the whole of the structural side of oxime chemistry is in a somewhat uncertain state and it seems doubtful whether the Hantzsch-Werner steriochemical hypothesis is adequate to explain the existence of the various isomers of oximes.[10]

The Beckmann change has been considered from a more general point of view in a recent paper [11] in which the change is considered to include such rearrangements as those of the Hofmann, Curtius and Lossen types. The fundamental transformation which stands out as essential to all such reactions is that some radical, R, attached to a carbon atom in the original compound, is found in combination with a nitrogen atom after the rearrangement has occurred. If oximes are excluded, the following general formula represents such changes.



The symbols a and b stand for R_2, $O=$, $HN=$, and similar groups, while x and y stand for H, Cl, Br, OH, and OCOR; in the azides, $N_2=$ takes the place of x and y. The mechanism of these changes is regarded as a separation of the radical R from the carbon atom and a wandering to the nitrogen atom under the influence of electrical constraint brought about by the necessity for redistribution of electrons to form the more stable system represented by the final stage.

Other Molecular Rearrangements

Derick has made several studies [12] of molecular rearrangements and has shown that his criterion, namely, that non-reversible intramolecular

[7] Hantzsch, *Ber.*, **24**, 13 (1891).
[8] Meisenheimer, *Ber.*, **54**, 3206 (1921); see also *ibid.*, **57**, 276, 282, 289 (1924).
[9] Beckmann, Liesche and Correns, *Ber.*, **56**, 341 (1923); Auvers and Ottens, *ibid.*, **57**, 446 (1924); Brady and Bishop, *J. Chem. Soc.*, **127**, 1357 (1925).
[10] Atack, *J. Chem. Soc.*, **119**, 1175 (1921); *idem*, *Ann. Rep. Prog. Chem.*, **1924**, 111.
[11] Jones and Scott, *J. Am. Chem. Soc.*, **44**, 407 (1922).
[12] See Derick and Bornmann, *J. Am. Chem. Soc.*, **35**, 1269 (1913).

rearrangements take place in the direction to decrease the ionization constant, holds also for the Beckmann transformation. He has also studied the Hofmann rearrangement from the same standpoint [13] and agrees with Hofmann's conclusions.[14] Hofmann showed that methylaniline hydrochloride rearranged to *p*-toluidine hydrochloride under the influence of heat and suggested that methyl chloride was dissociated and then added again, the reaction going through the formation of dimethylaniline. However most of the work on the Hofmann type of reaction is qualitative in character [15] and no kinetic studies appear to have been made.

The Mechanism of Halogenation

The active agent in aqueous halogenation has been the subject of considerable investigation recently,[16] and is still quite uncertain. Bromination in aqueous solution is usually considered to be due to the presence of hypobromous acid, since it is very much faster than bromination in anhydrous media; also aqueous bromination is markedly slower in presence of hydrobromic acid, which would reduce the concentration of hypobromous acid; and finally, the reaction of ethylene bonds with bromine water frequently (p. 139) gives considerable amounts of bromohydrin compounds. Cofman has studied the iodination of phenols and concludes that hypoiodous acid is the active iodinating agent common to all of the methods. He suggests that the hypoiodous acid may dissociate into positive iodine ions which may bring about the iodination. Baines studied the bromination of phenol and concluded that the difference in behavior in aqueous and non-aqueous solutions could be explained by postulating that hypobromous acid reacted in aqueous solution. He showed that hypobromous acid and phenol gave tribromophenol, and emphasized the fact [18] that in presence of concentrated hydrobromic acid, bromine is absorbed only slowly by phenol.

Soper and Smith have made a kinetic study of the halogenation of phenols and conclude that the halogenating agent cannot be the positive halogen ion. The reaction rate between phenol and hypochlorous acid is proportional to the concentrations of the two reactants and is also

[13] Howard and Derick, *J. Am. Chem. Soc.*, **46**, 166 (1924).
[14] Hofmann, *Ber.*, **4**, 742 (1871).
[15] See Schroeter, *Ber.*, **42**, 2336 (1909); Stieglitz, *ibid.*, **43**, 784 (1910); Montagne, *ibid.*, **43**, 2014 (1910); Rinkes, *Rec. trav. chim.*, **39**, 200 (1920).
[16] Stark, *Ber.*, **43**, 670 (1910); Cofman, *J. Chem. Soc.*, **115**, 1040 (1919); Baines, *ibid.*, **121**, 2810 (1922); Francis, *J. Am. Chem. Soc.*, **47**, 2340 (1925); Soper and Smith, *J. Chem. Soc.*, **129**, 1582 (1926).
[17] See also Pope and Wood, *J. Chem. Soc.*, **101**, 1823 (1912).

greatly affected by the acidity or alkalinity of the solution. In acid or in dilute alkaline solutions (hydroxyl-ion concentration in the neighborhood of 10^{-1}) the reaction rate is proportional to the hydroxyl-ion concentration until it becomes too fast for measurement. In more strongly alkaline solution (hydroxyl-ion concentration about 10^{-2}), the rate decreases to measureable dimensions and is now inversely proportional to the hydroxyl-ion concentration.

The authors explain this behavior by showing that the reaction very probably takes place between the phenoxide ion and the hypochlorous acid; by causing increased ionization, the addition of alkali would first increase and then decrease the rate. They also found that chlorine reacts with a phenol more rapidly than does hypochlorous acid. Since the rate of interaction of a phenol and hypochlorous acid is proportional to the product of the concentrations of the un-ionized acid and the phenoxide ion, the halogenating agent cannot be the positive halogen ion, because from the equilibrium,

$$HOCl \rightleftarrows OH^- + Cl^+$$

the concentration of the halogen ion is inversely proportional to the concentration of the hydroxyl ion. The authors conclude that the idea must also be abandoned in the case of chlorine because its rate of chlorinating acetaniline [18] for example, is independent of the excess of chloride ions present.

Francis has recently studied the action of bromine on basic compounds such as aniline and the toluidines, with a view to determining the active agent in aqueous brominations. He rejects the view that hypobromous acid is the reactant because when aniline reacts with hypobromous acid, grey and partly colloidal precipitates are obtained, whereas slightly acidified bromine water gives a white crystalline precipitate of tribromoaniline. He also showed that the bromination of *m*-nitrophenol by means of free bromine water is nearly one thousand times as rapid as that under similar conditions with hypobromous acid from which the bromine had been completely removed by silver sulfate. He showed also that this ratio holds for other organic compounds and even for inorganic substances such as potassium iodide. He concludes that the active agent is the same in both cases and consists of bromine atoms probably with positive charges.

It may be noted that while Soper and Smith's conclusions are against the idea of an active positive halogen they show that on the

[18] See Orton and King, *J. Chem. Soc.*, **109**, 1369 (1911).

basis of this idea bromine should be 5×10^5 times more active as a brominating agent than hypobromous acid, and, considering the nature of the measurements, this is comparatively near to the measured value of 10^3. If we assume the existence of such equilibria as

$$\begin{aligned} HOBr &\rightleftarrows OH^- + Br^+ \\ Br_2 &\rightleftarrows Br^- + Br^+ \end{aligned}$$

we have

$$\frac{K_{Br_2}}{K_{HOBr}} = \frac{[Br^+]\,[Br^-]}{[Br_2]} \Big/ \frac{[OH^-]\,[Br^+]}{[HOBr]} = \frac{[Br^-]\,[HOBr]}{[Br_2]\,[OH^-]}$$

Multiplying above and below by $[H^+]$ we obtain,

$$\frac{K_{Br_2}}{K_{HOBr}} = \frac{K_J}{K_W} = \frac{5 \times 10^{-9}}{10^{-14}} = 5 \times 10^5,$$

where K_J is the hydrolysis constant of bromine. We must regard the question of the active agent in aqueous halogenations as still open.

Structure and Chemical Reactivity

Recently there have been a number of systematic attempts to correlate structure and the reactivity of atoms and groups in organic compounds, and a considerable literature has grown up on this subject.[19] This line of work is justified in that a knowledge of the relationship between the structure of organic compounds and their reactivity is the basis for all synthetic work in organic chemistry. Adkins and Adams point out that there are two unrelated phases to this problem and in consequence there is considerable confusion as to the meaning of the word "reactivity." The first phase has to do with the extent to which a reaction goes and is ordinarily measured by the free energy change of the reaction. Michael wished to restrict the use of the term reactivity to this first phase of the problem, but most chemists have used the term in connection with the speed of the reaction and it will be used in that sense throughout this discussion. Michael, indeed, realized that the two factors are distinct relations as is evident from his own results on the reactivities of carboxyl derivatives. He points out that previous workers often use the two terms indiscriminately.[20]

[19] Adkins and Adams, *J. Am. Chem. Soc.*, **47**, 1368 (1925); Norris and Ashdown, *ibid.*, **47**, 837 (1925); Conant and Kirner, *ibid.*, **46**, 232 (1924); Conant and Hussey, *ibid.*, **47**, 476 (1925); Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925); Michael, *ibid.*, **41**, 393 (1919); Hill and Hibbert, *ibid.*, **45**, 3108, 3117, 3124 (1923); Hibbert and Timm, *ibid.*, **46**, 1283 (1924); Rice and Fryling, *ibid.*, **47**, 379 (1925).

[20] Petrenko-Kritschenko, *Ann.*, **341**, 150 (1905); *idem*, *Ber.*, **39**, 1454 (1906)

One way of studying the inter-relation between the structure of organic compounds and the affinity manifested at a given linkage, is to note the connection between the structure and the ionization or affinity constant of organic acids.[21] While many interesting facts and applications of this association have been noted, Adkins and Adams are of the opinion that "conclusions as to the relationship between the structure and the ionization of acids would appear to be of questionable value for interpreting organic processes. The factors which promote the separation of a positive electron (hydrogen ion) from a molecule may have little relationship to those factors which weaken or strengthen the linkages of carbon—carbon and of carbon—oxygen. Ionization of any type appears to play an unimportant rôle in organic reactions."

Norris and Ashdown in considering the relation between reactivity and chemical constitution emphasize the fact that reaction velocities are markedly affected by the conditions under which the reactions take place. The possible presence of unsuspected catalysts has led chemists to accept with caution any conclusions based on comparative velocities. The authors, therefore, made a particular study of the factors that influence the rate at which a definite reaction proceeds. These include temperature, presence of a catalyst and its concentration, the medium in which the reaction takes place (the solvent), the concentration, the possibility of side reactions, the formation of an intermediate complex between the reacting substances (the concentration of which determines the rate of the reaction), and the possibility that the concentration of such a complex varies as the result of a reversible reaction in which the equilibrium shifts as the concentration of the reactants changes. In order to obtain comparable results with a series of compounds, all of these conditions must be as nearly alike as possible and the mechanism of the several reactions must be identical.

Chemical Reactivity in the Acetal Reaction

We may now consider the methods used and results obtained in the study of particular classes of compounds in which the object is to measure quantitatively the chemical reactivity. Adkins and Adams made a complete study of the acetal reaction, which for acetaldehyde and ethyl alcohol may be represented

$$CH_3CHO + 2C_2H_5OH \rightleftarrows CH_3CH(OC_2H_5)_2 + H_2O.$$

They studied both the affinity changes and also the variation of reaction rate when both aldehyde and alcohol were varied.

[21] See Derick, *J. Am. Chem. Soc.*, 33, 1152 (1911).

TABLE XXII

ACETAL FORMATION—VARIATION WITH DIFFERENT ALCOHOLS

Acetal	ΔF	$k \times 10^3$
Methyl acetal	1452	1.02
Ethyl acetal	1549	2.37
n-Propyl acetal	1464	2.11
iso-Propyl acetal	2895	5.52
n-Butyl acetal	1115	2.68
iso-Butyl acetal	1112	1.93
sec-Butyl acetal	2641	4.64
tert-Butyl acetal	3867	11.34

Table XXII shows the effect of varying the alcohol but using the same aldehyde. When carbon atoms are substituted for hydrogen on the carbinol carbon atom the affinity values decrease very markedly, whereas substituting the 2-carbon atom of alcohols has little effect. In agreement with common experience there is no apparent relation between the affinity value and the chemical reactivity as measured by reaction rate. Methanol is abnormal, showing the slowest rate of all the alcohols; the secondary alcohols and especially the tertiary alcohols show a very much higher rate of reaction.

Table XXIII shows the effect of varying the aldehyde and the results are parallel to those obtained by varying the acid. Aldehydes that have a double bond in the 2-3 position, such as benzaldehyde, cinnamic aldehyde and furfural, have a very low affinity in the acetal reaction but on the other hand they react hundreds of times faster than do the lower aliphatic aldehydes.

TABLE XXIII

ACETAL FORMATION—VARIATION WITH DIFFERENT ALDEHYDES

Acetal	ΔF	$k \times 10^3$
Ethyl acetal	1549	2.37
Ethyl propylal	1657	2.09
Ethyl *n*-butylal	1413	1.91
Ethyl *iso*-butylal	2340	1.56
Ethyl furfurylal	3728	100.

Chemical Reactivity of Alcohols

Norris and Ashdown have made a quantitative study of the relative reactivities of the hydroxyl-hydrogen in alcohols by measuring the rate of reaction between an alcohol and an acyl chloride. In this reaction the hydrogen-oxygen bond is the only one in the alcohol which is involved. The reactions were carried out in ethereal solution, the

initial concentrations being approximately one molar. The acyl chloride selected was *p*-nitrobenzoyl chloride, because it could be prepared readily in a pure condition and it reacted at a convenient rate at 25°. The reaction gave a fairly good bimolecular constant up to about 40 per cent conversion, so that we may assume that the reaction is the simplest possible and involves only the union of the hydroxyl hydrogen with the chlorine atom of the acyl chloride.

TABLE XXIV

ALCOHOLS AND *p*-NITROBENZOYL CHLORIDE IN ETHER

Alcohol	Relative Rate	Alcohol	Relative Rate	Alcohol	Relative Rate
Methyl	100	*n*-Butyl	40.2	Benzyl	9.3
Ethyl	45.7	*iso*-Butyl	16.7	*β* Phenylethyl	21.6
Propyl	35.9	*sec*-Butyl	4.0	*γ*-Phenylpropyl	10.7
iso-Propyl	5.4	*tert*-Butyl	1.46		

Table XXIV shows the relative rates of a series of alcohols; the actual value of the constant for methyl alcohol at 25° is 0.184. Here we find that increasing the length of the chain up to the butyl group diminishes the reactivity, but after we pass the third bond successive lengthening of the chain produces alternately increase and decrease in reactivity. The introduction of side chains diminishes the reactivity, the effect being especially pronounced at the carbinol carbon atom.

Chemical Reactivity of Halides

Conant and his co-workers have investigated the relative chemical reactivities of organic halides. They selected an almost ideal reaction for that purpose. A simple metathesis occurs fairly rapidly with potassium iodide and a variety of organic halides.[22] The reaction is carried out in absolute acetone solution and is free from simultaneous reactions:

$$RCl + KI = RI + KCl.$$

Table XXV shows the relative rates for a series of alkyl chlorides, the results being reliable within ± 10 per cent. It is noteworthy that not

TABLE XXV

SUMMARY OF RESULTS FOR REACTION: RCl + KI = RI + KCl

Compound	k_{60}	Compound	k_{60}
CH_3CH_2Cl	0.196	*n*- $C_{20}H_{41}Cl$	0.089
n- C_8H_7Cl	.104	*iso*- $C_5H_{11}Cl$	.068
n- C_4H_9Cl	.101	$(CH_3)_2CHCl$	.0015
n- $C_5H_{11}Cl$	.128	$C_2H_5CHClCH_3$	.0022
n- $C_6H_{13}Cl$	.125	$CH_3CH_2CH_2CHClCH_3$	.0048
n- $C_7H_{15}Cl$	.122	$(CH_3)_3CCl$	.0018
n- $C_{14}H_{29}Cl$	.098	$C_6H_{11}Cl$ (cyclohexyl chloride)	.0001

[22] See Finkelstein, *Ber.*, 43, 1528 (1910).

only these but also the great variety of other halogen derivatives studied have all the same temperature coefficients, although the different substances may differ a millionfold in reactivity. The average value of Q calculating from the equation $\frac{d \ln k}{dT} = \frac{Q}{RT^2}$, is 18,800 calories. Sodium or lithium iodides may be substituted for the potassium iodide without changing the reaction rate or the temperature coefficient.

With primary straight chain compounds containing three or more carbon atoms, there is but little change from propyl to myricyl ($C_{30}H_{61}Cl$), the slight changes in reactivity being merely second order effects when compared with changes in reactivity caused by changes in structure. The striking contrast between the primary chlorides on the one hand and the secondary and tertiary compounds on the other is at once apparent; both the secondary and tertiary chlorides are much less reactive than the corresponding primary compounds, although the secondary and tertiary chlorides do not differ very much in reactivity from each other. Cyclohexyl chloride is most peculiar in that its reactivity is too low to be measured.

Conant and Hussey [19] compare their results with previous work on the reactivity of alkyl halides with other substances [23] and conclude: "For purposes of expressing numerically the factors governing the behavior of organic substances as we deal with them in the laboratory, differences in reactivity of 25 or even 50 per cent are of relatively little importance. Variations of threefold, a hundredfold and a millionfold are the cause of vagaries which make our present structural formulas so often unreliable in predicting reactions. From this point of view the results of all previous studies of *primary* halides and data here presented may be said to be in general agreement. *In a great variety of reactions a methyl halide is 5 to 20 times more reactive than the ethyl compound, which in turn is only about twice as reactive as the other primary straight chain compounds that do not differ materially from one another, at least as high in the series as* $C_{30}H_{61}Cl$. The forking of the chain diminishes the reactivity of primary compounds, which diminution in the case of amyl is about 100 per cent."

Conant, Kirner and Hussey [19] investigated the reaction velocity for substances of the type ACH_2Cl where A is one of the so-called negative groups such as carboxyl, carbethoxy, or phenyl, and a summary of the

[23] Burke and Donnan, *J. Chem. Soc.*, **85**, 555 (1904); Hecht, Conrad and Brückner, *Z. physik. Chem.*, **4**, 273 (1889); Segaller, *J. Chem. Soc.*, 103, 1154 (1913); Menschutkin, *Z. physik. Chem.*, **5**, 589 (1890).

results is given in Table XXVI. It will be seen that the reactivity of the halogen atom in a series of compounds of the type ACH_2Cl is more or less proportional to the activity of the α-hydrogen atom in a similar series of the type ACH_3; that is, the so-called negativity determines the activity of both the α-hydrogen and the α-halogen atoms. It is of interest also to compare the series of compounds CH_3COOCH_2Cl (10.8), $CH_3COOCH_2CH_2Cl$ (0.018), and $CH_3COOCH_2CH_2CH_2Cl$ (1.6), which illustrates the manner in which the influence of an unsaturated group is transmitted through a chain of carbon atoms. All of these compounds are very much more reactive than the alkyl halides, a fact

TABLE XXVI

SUMMARY OF RESULTS FOR REACTION: RCl + KI = RI + KCl

Compound	k_{30}	Compound	k_{30}
$C_6H_5COCH_2Cl$	4190	$C_6H_5CH_2Cl$	7.9
CH_3COCH_2Cl	1428	NH_2COCH_2Cl	3.9
$CNCH_2Cl$	123	CH_2CHCH_2Cl	3.2
$C_2H_5COOCH_2Cl$	68.9	C_2H_5OOCCl	1.0
CH_3OCH_2Cl	36.7	$CH_3CH_2CH_2CH_2Cl$	.4
C_6H_5COCl	28	$(C_6H_5)_3CCl$	1520
CH_3COOCH_2Cl	10.8	$(C_2H_5OOC)_2CHCl$	2420
$C_6H_5COCH_2CH_2CH_2Cl$	9.3		

which is not consistent with Fluorscheim's hypothesis of alternate strong and weak valences. There is, however, alternating reactivity which would be expected from certain theories of valence.

Chemical Reactivity of Ketones

Rice and Fryling[19] have recently examined the reactivity of the saturated aliphatic ketones towards iodine, this being a repetition and extension of earlier studies made by Lapworth and by Dawson and his co-workers.[24] This reaction is catalyzed by hydrogen ions and consists of some kind of slow measurable activation of the ketone followed by instantaneous iodination. The conclusion is based on the facts that the rate of the reaction is entirely independent of the concentration of the halogen and is also entirely independent of the particular halogen employed, chlorine, bromine and iodine giving exactly the same velocity. The results are given in Table XXVII, from which it will be seen that the changes in reactivity caused by the substitution of alkyl radicals are comparatively insignificant. By substituting all three hydrogens of one of the methyl groups of acetone we only slightly more than halve the velocity. The reactivity of organic compounds containing the carboxyl

[24] Lapworth, *J. Chem. Soc.*, **85**, 30 (1904); Dawson and Leslie, *ibid.*, **95**, 1860 (1909); Dawson and Wheatley, *ibid.*, **97**, 2048 (1910); Dawson and Ark, *ibid.*, **99**, 1740 (1911).

TABLE XXVII

REACTION BETWEEN KETONES AND IODINE IN AQUEOUS SOLUTION CATALYZED BY HYDROCHLORIC ACID

Ketone	k_{25} (±5%)	Ketone	k_{25} (±5%)
CH_3COCH_3	17.1	$CH_3COCH_2CH_2CH_2CH_3$	23.1
$CH_3COCH_2CH_3$	20.9	$CH_3COCH_2CH(CH_3)_2$	18.
$CH_3CH_2COCH_2CH_3$	17.1	$CH_3COC(CH_3)_3$	7.7
$CH_3COCH_2CH_2CH_3$	19.4	$CH_3CH_2COCH_2CH_2CH_3$	18.
$CH_3COCH(CH_3)_2$	17.	Cyclohexanone[a]	142.

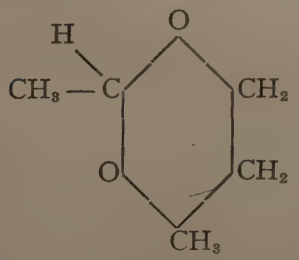
[a] This measurement was made by Mr. John McGraw, Jr., in the author's laboratory.

group has also been investigated by Michael, Petrenko-Kritschenko, and Stewart.

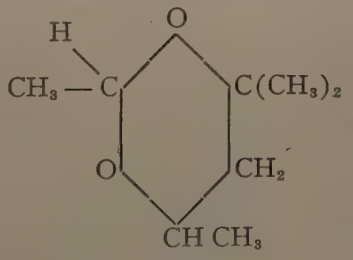
Chemical Reactivity of Cyclic Acetals

Hill and Hibbert [19] have made a study of the preparation of cyclic acetals by treating a polyhydroxy compound with acetylene in presence of a small amount of mercuric sulfate and concentrated sulfuric acid as a catalyst. By means of partition experiments in which one molecular weight of acetylene is passed into a mixture of one molecular weight of each of two different glycols, we may obtain a measure of the relative ease of formation of the two ring systems from the amounts of the two cyclic acetals formed. The authors found that when one mole of acetylene reacts with one mole each of ethylene glycol and trimethylene glycol, the ratio of the 6-membered structure to the 5-, is approximately two to one. A similar experiment involving a partition of one mole of acetylene between one mole each of ethylene glycol and tetramethylene glycol showed that the penta-atomic ring is formed three times as readily as the acetal containing 7 ring atoms. The ease of formation, therefore, increases from the 5- to the 6-membered rings and then diminishes again with the 7-.

Experiments in which the formation of similar rings was studied showed that the presence of methyl groups attached to the glycol carbon atoms favors cyclization. Thus II is formed in preference to I in the



I



II

ratio of two to one.

Homogeneous Gas Reactions

In the last year or two several homogeneous reactions in the gas phase[25] have been studied. Although the actual examples are not catalytic it is obvious that such studies will throw much light on the mechanism of reaction kinetics and should therefore be included in any discussion of homogeneous reactions. Smith has studied the rate of racemization of pinene and found it to be a first order homogeneous reaction. The rate of change was measured in the gaseous and pure liquid phases, and in solution in petroleum, acetophenone, and α-methylnapthalene. The constants are nearly the same even when the concentration is varied over a thousandfold from the gas to the pure liquid reaction. The reaction goes at a measurable rate at temperatures near 200° and the heat of activation as calculated from the Arrhenius equation is 43,710 calories per gram-molecule. These experiments are of considerable interest since they are the first measurements of a racemization rate in the gas phase and such reactions are without heat effect and are perfectly symmetrical, the corresponding forward and reverse rates being equal.

Hinshelwood and his co-workers have studied the rates of several organic decompositions in the gaseous phase. Two of these, acetone and propionic aldehyde, have proved to be unimolecular and only slightly affected by the walls of the vessel. Acetaldehyde is homogeneous but bimolecular. Certain other decompositions such as the reaction $HCOOCH_3 = CH_4 + CO_2$ were found to be largely heterogeneous and no attempt was made to isolate the homogeneous reaction from the surface reaction.

The velocity of decomposition of acetone is conveniently measurable between 500° and 600°. It obeys the usual criteria of a homogeneous unimolecular reaction, in that (*a*) the rate is independent of the surface of the containing vessel, since the addition of silica powder left the reaction rate unchanged, and (*b*) the time taken for any fraction of the total change to complete itself is independent of the initial pressure. Hinshelwood considers that the primary decomposition of acetone is a process in which the two methyl groups fly off from the carboxyl group and unite to form ethane or methane and hydrogen. A small amount of carbon dioxide and ethylene is formed but analysis of the gaseous products supports this scheme. It is in marked contrast to the pyrogenic

[25] Smith, *J. Am. Chem. Soc.*, **49**, 43 (1927); Hinshelwood and Hutchison, *Proc. Roy. Soc.*, **111A**, 245, 380 (1926); Hinshelwood and Thompson, *ibid.*, **113**, 221 (1926).

decomposition of acetone in a pyrex tube to yield ketene [26]: $CH_3COCH_3 = CH_2:CO + CH_4$. This reaction occurs at temperatures between 400° and 700° but appears to be heterogeneous since the pyrex tube is greatly corroded during the course of the reaction. The heat of activation of the homogeneous reaction is 68,500 calories. The decomposition of propionic aldehyde also was found to be mainly a homogeneous unimolecular reaction; however, at pressures below 80 mm. of mercury, the velocity constant falls off appreciably. The heat of activation is 55,000 calories.

Acetaldehyde at about 500° decomposes smoothly into methane and carbon monoxide and the reaction is homogeneous but bimolecular. The heat of activation in this case is 45,500 calories (for two gram-molecules).

Examples of catalysis occurring in homogeneous organic systems in the gaseous state seem to be almost non-existent. Thus the esterification of acetic acid in the vapor phase occurs with extreme slowness [27] unless catalytic oxides are present. Further keto-enol isomers do not change over in the vapor phase (p. 94) although these reactions are extremely susceptible to catalytic influence.

[26] Hurd and Tallyn, *J. Am. Chem. Soc.*, **47**, 1427 (1925); Schmidlin and Bergman, *Ber.*, **43**, 2821 (1910).
[27] Milligan, Chappell and Reid, *J. Phys. Chem.*, **28**, 872 (1924).

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